EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	C.A. No. 05-356-KAJ (consolidated)

OPENING EXPERT REPORT OF DR. JEFFREY L. CUMMINGS

I. ACADEMIC AND PROFESSIONAL QUALIFICATIONS

A. Experience and Credentials

1. I am a Professor of Neurology and a Professor of Psychiatry and Biobehavioral Sciences at the University of California – Los Angeles. I am the Augustus S. Rose Professor of Neurology; the Director of the UCLA Alzheimer's Disease Center; the Director of the Deane F. Johnson Center for Neurotherapeutics; and the Executive Vice-Chair of the Department of Neurology at the David Geffen School of Medicine.
2. I have treated patients, taught courses, and written extensively on the symptoms and causes of Alzheimer's Disease ("AD"), including its behavioral aspects. I also developed the Neuropsychiatric Inventory ("NPI"), which is the most widely-used testing method for evaluating neuropsychiatric behavior associated with AD.
3. I was awarded a Baccalaureate in zoology from the University of Wyoming in 1970 and an M.D. from the University of Washington School of Medicine in 1974. I subsequently completed an internship at the Hartford Hospital, followed by residency

in neurology at the Boston University School of Medicine and fellowships in behavioral neurology there and at the National Hospital for Neurological Diseases (London).

4. I am licensed to practice medicine in California. I am also a certified member of the National Board of Medical Examiners and of the American Board of Neurology and Psychiatry (Neurology).

5. I have been associated with UCLA since 1980, when I joined the faculty of the UCLA School of Medicine as Assistant Professor of Neurology in Residence. I became the Clinical Co-Director of UCLA's Alzheimer's Disease and Memory Disorders Clinic in 1985, a position I held until 1991, when I became Director of both the UCLA Geriatric Behavioral Neurology Clinic and the UCLA Alzheimer's Disease Center. I am also presently Director of the Deane F. Johnson Center for Neurotherapeutics at UCLA as well as Executive Vice Chair of the Department of Neurology.

6. I also had a long association with the Department of Veterans Affairs. In 1980, I joined the VA as Director of the Neurobehavior Unit of the West Los Angeles Veterans Affairs Medical Center (Brentwood Division), a position I held until 1990. In addition, from 1981 to 1988, I was Chief of Medicine, West Los Angeles VAMC (Brentwood Division), and from 1984 to 1988, Assistant Clinical Director for the Nursing Home Care Unit of the West Los Angeles VAMC. From 1986 to 1991, I was Co-Chief of the Movement Disorders Laboratories, West Los Angeles VAMC (Brentwood Division), and from 1989 to 1996, the Associate Chief of Psychiatry for Neurobehavior, West Los Angeles, VAMC. From 1992 to 1999, I was the Director

of the VA Geriatric Neurology Fellowship, West Los Angeles VAMC, and from 1996 to 1999, a consultant to the Neurobehavior Unit, Psychiatry Service, West Los Angeles VAMC.

7. Over the past two decades, I have written or co-authored more than 450 academic articles, over 20 textbooks, 5 yearbooks, 15 multi-center publications, 175 book chapters, 5 monographs, 262 abstracts, 16 book reviews, and 6 forewords pertaining to various aspects of neurology and psychiatry, including AD.

8. My research has also included participation in a number of industry-sponsored projects and clinical trials concerning AD, including: acetyl-l-carnitine (Sigma Tau Pharmaceutical Co.); DuP 996 (DuPont-Merck Pharmaceutical Co.); tacrine (Parke-Davis); ondansetron (Glaxo Pharmaceuticals); metrifonate (Miles-Bayer); milameline (Miles-Bayer); donepezil (Pfizer and Eisai); xanomeline (Lilly); olanzapine (Lilly); rivastigmine (Novartis); galantamine hydrobromide (Janssen); neotrofin (Neurotherapeutics); SR57746A (Sanofi-Synthelabo).

9. I have also participated in foundation-sponsored Alzheimer's research and the National Institute on Aging's Alzheimer's Disease Cooperative Study ("ADCS") trials, including studies of: testosterone (ISOA and the French Foundation); rofecoxib and naproxen (ADCS); simvistatin (ADCS); homocysteine (ADCS); curcumin (ISOA and the French Foundation); and valproate (ADCS).

10. During my career, I have been on the editorial boards of many academic journals and textbooks, including: Alzheimer's Disease Management Today (Chair Editorial Board); Yearbook of Geriatrics and Gerontology (Associate Editor); Journal of Neuropsychiatry and Clinical Neuroscience (Associate Editor); Psychosomatics

(Associate Editor); Current Psychiatry Report (Associate Editor); Current Psychiatric Report (Associate Editor); Psychosomatics (Associate Editor); Current Psychiatry Report (Associate Editor); Alzheimer's Disease and Associated Disorders; American Journal of Alzheimer's Disease; Archivos de Neurosciencias; Behavioral Neurology; Caring for the Aged; Clinical Geriatrics; CNS Spectrums; Cognitive and Behavioral Neurology; Cognitive Sciences; Dementia and Geriatric Cognitive Disorders; Demenze; Health in Mind and Body; Internal Medicine Thailand; International Journal of Neuropsychopharmacology; Journal of the American Geriatric Society; Journal of the American Medical Directors Association; Journal of Geriatric Psychiatry and Neurology; Long-Term Care Forum; Middle-Eastern Journal of Age and Aging; Middle-Eastern Journal of Family Medicine; Neurocase; Neurology; Neuropsychiatric Disease and Treatment; Neuropsychiatry, Neuropsychology and Behavioral Neurology; Neuropsychology; Practical Neurology; Psychiatric Times; Psychogeriatrics; Textbook of Neuropsychiatry, 2nd Edition; Trends in Evidence Based Neuropsychiatry; the Economics of Neuroscience; and Neuropsychiatric Disease and Treatment.

11. I am a regular reviewer of many academic journals, including: Alzheimer's Disease and Associated Disorders; American Journal of Psychiatry; American Journal of Geriatric Psychiatry; Annals of Neurology; Archives of Neurology; and Neurology. I have also reviewed scientific articles for other well-known journals, including: Archives of General Psychiatry; Biological Psychiatry; General Hospital Psychiatry; International Psychogeriatrics; Journal of Clinical Psychiatry; Journal of Geriatric Psychiatry and Neurology; Journal of the International Neuropsychological Society;

Journal of Neurology, Neurosurgery and Psychiatry; Journal of the American Geriatrics Society; Journal of the American Medical Association; Journal of Neuroscience; Lancet; Movement Disorders; NeuroImage; Neuron; Neuropsychiatry, Neuropsychology, and Behavioral Neurology; New England Journal of Medicine; Science and Stroke.

12. I am, or have been, a member of many societies and associations relating to Neurology, including the American Neurological Association; the American Academy of Neurology; International Neuropsychological Society; Behavioral Neurology Society; American Psychiatric Association; Society of Biological Psychiatry; American Geriatric Society; Movement Disorders Society; American Neuropsychiatric Association; UCLA Brain Research Institute; American Association for the Advancement of Science; Society for Neuroscience; American Medical Association; Collegium Internationale Neuropsychopharmacologium; American Association of Geriatric Psychiatry; Neuropsychiatric Institute, UCLA; Institute of Brain Aging and Dementia, UCI; Institute for Neurodegenerative Disease, UCSF; International College of Geriatric Psychoneuropharmacology; International Psychogeriatric Association; American College of Neuropsychopharmacology; American Society for Experimental Neurotherapeutics (ASENT); Egyptian Neurological Society; and the Thai Neurological Society.

13. I have also provided consulting services to many pharmaceutical companies and other industry groups, including: Acadia; AstraZeneca; Avanir; Aventis; Bayer; Best Practices Consulting; Biomedisyn; Bristol-Myers Squibb; Cognishunt; Council of Advisors; Eisai; EnVivo; GlaxoSmithKline; Janssen; Lilly; Lundbeck International;

Memory Pharm; Merz; Myriad; Neurochem; Neurotrax; Novartis; Ono; Parke Davis; Pfizer; Sanofi-Aventis; Praecis; Sandoz; Searle; Sepracor; Synx-pharma; Takeda; Voyager; Wyeth; and Zeneca.

14. I have received a number of prestigious research and teaching awards during my career, including: the Arthur Cherkin Award for contributions to Geriatrics and Gerontology at UCLA (1989); the Neurology Faculty Teaching Award (1990); a Research Award from the Alzheimer's Association (1992); the Psychiatry Senior Faculty Teaching Award (1993); Award for the Best Doctors in America – Neuropsychiatry Section (1993, 2001) and Neurology Section (1996); Irving and Helga Cooper Award for Geriatrics Research (1993); Nor-Age, Pharmacia & Upjohn Award (1996); The Augustus S. Rose Endowed Chair (1996); Honorary Member of the American Association of Geriatric Psychiatry (1997); the Gold Hugo Award (1999); Cotzias Lecturer, Spanish Neurological Society (2000); Honoree, Alzheimer Association of Orange County (2000); Elected Member of the American College of Neuropsychopharmacology (2002); 23rd Srinivasan Orator with medal (2003); Henderson Lectureship, American Geriatric Society (2005); and the Outstanding Alumni Award, University of Wyoming (2005).

15. Attached hereto as Exhibit A is a copy of my *curriculum vitae*.

B. Documents Considered

16. In reviewing the defendants' assertions and forming the opinions stated in my report, I relied upon my experience, my knowledge of the relevant literature and state of the art, and I also reviewed the materials set forth in Exhibit B.

C. Prior Testimony

17. The only pharmaceutical or patent related case in which I have testified as an expert at trial or by deposition within the last four years is Janssen-Ortho Inc. et al. v. Ratiopharm Inc. et al., Court File No. T-197-05. In addition, within the last four years, I have been deposed three or four times in cases (whose names I do not recall) involving the medical condition of individual patients.

D. Compensation

18. I am being compensated at my standard rate of $350 per hour. My compensation is not linked in any way to the outcome of this litigation.

II. SCOPE OF OPINION

19. I have been asked to review the assertions made by the defendants in the above-captioned action that U.S. Patent No. 4,663,318 (the '318 Patent") is invalid. I have been informed that the defendants have stipulated to infringement of claims 1 and 4 of the '318 Patent, and accordingly, I have focused on these two claims in considering the defendants' assertions.

20. I have also been informed about the so-called objective considerations of non-obviousness in the patent law and have been asked to form my own opinion about whether objective considerations of non-obviousness support the validity of the '318 Patent.

21. I have done these things and have formed the opinion described in this report. In brief, it is my opinion that objective considerations of non-obviousness do support the validity of the '318 Patent.

III. BACKGROUND

A. The '318 Patent

22. The patent is directed to a medical doctor treating elderly patients; that is, to a physician likely to encounter patients suffering from AD.

23. I believe that I am able to understand the patent as would a person of skill in the art in 1986 and to comment upon how such a person would have understood the prior art cited by defendants and other relevant information as of that date.

24. As a general matter, I understand the claims of the '318 patent to be directed to the treatment of AD, whether pre-senile on-set or Senile Dementia of the Alzheimer's Type ("SDAT"), using therapeutic doses of galantamine or its pharmaceutically-acceptable acid-addition salts, including galantamine hydrobromide. By treatment, I include alleviation of the symptoms of AD, particularly the cognitive loss that is the core feature of the disease.

B. Alzheimer's Disease

25. AD is an age-related and progressive brain disorder that occurs gradually and results in memory loss, behavior and personality changes, and a decline in thinking abilities. Additionally, individuals experience a decline in their ability to perform the activities of daily living (known as "ADLs").

26. AD is one of a group of disorders, termed dementias, that are characterized by cognitive and behavioral problems. Dementia is the loss of memory, reason, judgment, and language to such an extent that it interferes with a person's daily life and activities. Dementia is not a disease itself but a group of symptoms that often accompanies a disease or condition.

27. AD is the most common cause of dementia in the elderly. AD and the accompanying symptoms of dementia are not part of normal aging, but rather are caused by a disease that affects the brain. AD is a degenerative disease of the brain that produces progressive dementia characterized by memory loss, disorientation, language loss, and loss of self-care functions. The core feature of AD is progressive cognitive impairment with resultant loss of functional capacity.

28. In addition, most AD patients also experience noncognitive behavioral problems, such as depression, disruptive agitation, and psychosis. Behavioral symptoms are very common among patients with mild to moderate dementia of the Alzheimer's type and are a significant characteristic of the disease. It has been reported that 20 to 50 percent of patients with AD experience delusions, 10 to 25 percent have hallucinations, and 40 to 50 percent have symptoms of depression. Other non-cognitive behavioral changes in AD patients include anxiety, personality changes, sleep disturbances, appetite changes, and alterations in sexual behavior. These are neuropsychiatric symptoms associated with AD.

29. The neuropsychiatric symptoms associated with AD result in increased distress to patients and caregivers, premature institutionalization, increased cost of care, and significant compromise of the quality of life of patients and their families.

30. In an article entitled "Psychosis of Alzheimer's Disease and Related Dementias - Diagnostic Criteria for a Distinct Syndrome" by Drs. Dilip V. Jeste and Sandford I. Finkel, the authors observed that: "The very first patient with dementia described by Alzheimer had psychotic symptoms, including paranoid delusions and hallucinations. Subsequently, the term 'senile psychosis' was commonly used in the older literature

to refer to psychosis in elderly patients with dementia. Numerous studies of the prevalence and nature of psychotic symptoms have been conducted in patients with Alzheimer's disease (AD) and other dementias. Although some of this literature is limited by methodolog[y], ... more rigorous investigations have generally reported a frequency of psychotic symptoms in AD to be between 30% and 50%. In a recent study of 329 patients with AD, Paulsen et al. computed the cumulative 4-year incidence of new-onset psychosis of AD to be 51%. Once present, delusions recur or persist for several years in a majority of AD patients. Furthermore, a number of groups of researchers have found that delusions and hallucinations are commonly associated with aggression, agitation, and disruptive behavior in patients with AD. Psychotic symptoms are a major cause of caregiver distress and often result in institutionalization of the patients." (page 29).

31. The prevalence of dementia has been estimated to double every five years after the age of 60. Roughly one percent of those age 60 to 64 are affected, 2 percent of those age 65 to 69, 4 percent of those age 70 to 74, 8 percent of those age 75 to 79, 16 percent of those age 80 to 84, and 30 to 45 percent of those age 85 and older. Most of these cases of dementia are attributable to AD.

C. The Cause of AD

32. The ultimate cause of AD remains obscure, but it has long been known that the disease is characterized by two particular pathologic features: "plaques" and "neurofibrillary tangles."

33. Plaques are comprised of a central core of amyloid protein surrounded by degenerating nerve cells and inflammatory and brain-scar tissue components. Plaques begin as diffuse deposits of amyloid protein and mature to the form just

described. Amyloid is a naturally occurring protein whose accumulation in plaques is now understood to comprise the basic disease process.

34. Neurofibrillary tangles are comprised of abnormal tau protein in neurons twisted into paired helical filaments. These are visible microscopically in the nerve cells of the Alzheimer brain.

35. The consequence of these plaques and neurofibrillary tangles is now understood to lead to disruption of neurotransmitter systems, compromise of cell function, and ultimate cell death. At the time the patent was filed in January 1986, the existence of plaques and neurofibrillary tangles as markers of AD was known but their role in the disease was uncertain.

36. By 1986, it was known that AD was associated with a range of neurochemical deficiencies, including norepinephrine, serotonin, somatostatin, vasopressin, and ß-endorphin.

37. One of the most prominent features of AD is that levels of a neurotransmitter called acetylcholine (ACh) declines. Acetylcholine is crucial in the formation and retention of memory. By the late 1970s, it was known that levels of an enzyme used to produce acetylcholine (choline acetyl tranferase or ChAT) were markedly reduced in AD patients, and acetylcholine levels were thought to be reduced as well. In addition, by the early 1980s, AD had been associated with a degeneration of the nucleus basalis of Meynert ("nbM"), the portion of the brain in which the cortical pre-synaptic cholinergic neurons reside and in which choline acetyl tranferase is manufactured.

D. *Diagnosis of AD*

38. In January 1986, when the application for the '318 patent was first filed, a diagnosis of AD would have been made using one of two diagnostic criteria. The first,

published in 1980, is contained in the DSM III; the second was published in 1984 by a working group of the National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) and are referred to as the NINCDS-ADRDA criteria. As a general matter, practicing physicians would be more likely to use the DSM III criteria, and researchers those of NINCDS-ADRDA, but the diagnosis of any particular patient is likely to be the same using either set of criteria.

39. DSM III classifies AD along with the rarer Pick's Disease (now called Frontotemporal Dementia) as Primary Degenerative Dementia. The DSM III's diagnostic criteria for primary degenerative dementia are

a. "Dementia:

b. Insidious onset with uniformly progressive deteriorating course.

c. Exclusion of all other specific causes of Dementia by the history, physical examination, and laboratory tests."

40. The DSM III's diagnostic criteria for dementia are

d. "A loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning;

e. Memory impairment;

f. And at least one of the following:

i. Impairment of abstract thinking, as manifested by concrete interpretation of proverbs, inability to find similarities and differences between related words, difficulty in defining words and concepts and other similar tasks

ii. Impaired judgment

iii. Other disturbances of higher cortical function, such as aphasia (disorder of language due to brain dysfunction), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), "constructional difficulty" (e.g., inability to copy three-dimensional figures, reassemble blocks, or arrange sticks in specific designs).

g. State of consciousness not clouded (i.e., does not meet the criteria for delirium or intoxication, although these may be superimposed).

h. Either (i) or (ii):

i. evidence from the history, physical examination, or laboratory tests, of a specific organic factor that is judged to be etiologically related to the disturbance

ii. in the absence of such evidence, an organic factor necessary for the development of the syndrome can be presumed if conditions other than Organic Mental Disorders have been reasonably excluded and if the behavioral change represents cognitive impairment in a variety of areas."

41. NINCDS-ADRDA recommends a hierarchy of "definite," "probable," and "possible" Alzheimer's Disease for use in the clinical diagnosis of AD.

42. The criterion for the diagnosis of definite AD under NINCDS-ADRDA are the clinical criteria for probable AD, described below, and histopathologic evidence (*i.e.*, evidence from the study of the microscopic changes in diseased tissues) obtained from a biopsy or autopsy.

43. Probable AD under NINCDS-ADRDA.

a. The criteria for the clinical diagnosis of "probable AD" include:

   i. Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;

   ii. Deficits in two or more areas of cognition;

   iii. Progressive worsening of memory and other cognitive functions;

   iv. No disturbance of consciousness;

   v. Onset between ages of 40 and 90, most often after age 65; and

   vi. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

b. The diagnosis of probable AD is supported by:

   i. Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

   ii. Impaired activities of daily living and altered patterns of behavior;

   iii. Family history of similar disorders, particularly if confirmed neuropathologically; and

   iv. Laboratory results of normal lumbar puncture as evaluated by standard techniques; normal pattern or non-specific changes in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on a CAT scan with progression documented by serial observation.

c. Other clinical features consistent with the diagnosis of probable AD, after excluding other causes of dementia, include:

i. Plateaus in the course of progression of the illness;

ii. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; and

iii. Other neurologic abnormalities in some patients, especially with more advanced disease, and including motor signs such as increased muscle tone, myoclonus, or gait disorder.

d. Features that make the diagnosis of probable AD uncertain or unlikely include:

i. Sudden apoplectic onset;

ii. Focal neurologic findings such as hemiparesis (*i.e.*, weakness on one side of the body), sensory loss, visual field deficits, and incoordination (*i.e.*, lack of control over harmonious and voluntary muscle movement) early in the course of the illness; and

iii. Seizures or gait disturbances at the onset or very early in the course of the illness.

44. Possible AD under NINCDS-ADRDA. A clinical diagnosis of "possible AD":

a. May be made on the basis of the dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

b. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

c. Should be used in research studies when a single gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

45. The clinician diagnosing AD in January 1986 would have based the diagnosis on recognizing the clinical syndrome described, performing basic laboratory tests (generally thyroid, B-12, and syphilis), and possibly a CAT scan. The clinical diagnosis was usually accurate when compared to the autopsy diagnosis of those coming to post-mortem examination.

E. Stages of AD

46. Although the course of AD is not the same in every patient, the symptoms of the disease tend to develop over the same general stages, as described below.

47. Preclinical AD: Memory loss is the first apparent feature of mild cognitive impairment ("MCI"). MCI is often an initial, transitional phase between normal brain aging and AD.

48. Mild AD: As the disease begins to affect the cerebral cortex, especially the interior temporal regions, memory loss continues and changes in other cognitive abilities emerge. The clinical diagnosis of AD is usually made during this stage.

49. Signs of mild AD can include:

a. memory loss;

b. Confusion about the location of familiar places – getting lost begins to occur;

c. Taking longer to accomplish normal daily tasks;

d. Trouble handling money and paying bills;

e. Poor judgment leading to poor decisions;

f. Loss of spontaneity and sense of initiative; and

g. Mood and personality changes, increased anxiety.

50. Moderate AD: By moderate AD, Alzheimer damage has spread further to the areas of the cerebral cortex that control language, reasoning, and conscious thought. Affected regions continue to atrophy and signs and symptoms of the disease become more pronounced and wide-spread. Behavioral problems, such as wandering and agitation, can occur. More intensive supervision and care become necessary, and this can be difficult for many spouses and families.

51. The symptoms of Moderate AD can include:

    a. Increasing memory loss and confusion;

    b. Shortened attention span;

    c. Problems recognizing friends and as the disease progresses to severe, family members;

    d. Difficulty with language; problems with reading, writing, working with numbers;

    e. Difficulty organizing thoughts and thinking logically;

    f. Inability to learn new things or to cope with new or unexpected situations;

    g. Restlessness, agitation, anxiety, tearfulness, wandering – especially in the late afternoon or at night;

    h. Repetitive statements or movement, occasional muscle twitches;

    i. Hallucinations, delusions, suspiciousness or paranoia, irritability;

    j. Loss of impulse control and periods of agitation; and

    k. Perceptual-motor problems (such as trouble getting out of a chair or setting the table).

52. Severe AD. In severe AD, memory loss proceeds to include remote memories as well as an inability to learn new information. Language changes progress so that patients

are unable to comprehend much of what is said and have difficulty articulating any thoughts. Visuospatial abilities are severely compromised, and they may have difficulty finding their way in their own homes. Judgment and abstract reasoning are obliterated. Control of bladder continence begins to be impaired.

53. End Stage AD: As the patient approaches the end of AD, histopathologic evidence reveals that plaques and neurofibrillary tangles are widespread throughout the brain and areas of the brain have atrophied further. Patients cannot recognize family and loved ones or communicate in any way. They are completely dependent on others for care. All sense of self seems to vanish.

54. Other symptoms of End Stage AD can include weight loss; seizures; skin infections; difficulty swallowing; groaning, moaning or grunting; increased sleeping; and lack of bladder and bowel control.

IV. SUBJECT MATTER OF THE '318 PATENT

55. As indicated above, I understand that the defendants have stipulated to the infringement of two of the claims of the '318 patent, claims 1 and 4, and that those are the only claims at issue.

56. Claim 1 claims: "A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof."

57. Claim 4 claims: "A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day."

58. I have been asked to interpret the claims of the '318 Patent in the context of the patent and its prosecution history from the perspective of a person of ordinary skill in the art as of the date the patent application was filed, on January 15, 1986.

59. In my opinion, a person skilled in the art would have understood the elements of Claim 1 as follows:

a. "method of treating" means a method for reducing the symptoms or deferring the decline associated with AD, including the core feature of progressive cognitive impairment, in a manner beneficial to the patient;

b. "Alzheimer's disease or related dementias" would mean an illness diagnosed as AD, whether presenile onset AD or SDAT, likely in accordance with either the DSM III or the NINCDS-ADRDA criteria referenced above;

c. "therapeutically effective amount" is an amount sufficient to bring about a beneficial effect for the patient in the context of a method of treating AD;

d. "galanthamine or a pharmaceutically-acceptable acid addition salt thereof" would be understood to include galantamine itself (also spelled "galanthamine"), and certain acid addition salts, including galantamine hydrobromide.

60. Claim 4 would be understood as above, and additionally to require that the method of administration of the galantamine or pharmaceutically-acceptable acid addition salt thereof to be oral and to be in an amount between 10 and 2000 mg per day.

V. THE NEED FOR A TREATMENT FOR AD

A. Awareness of SDAT as an epidemic

61. Before the late 1960s, senility was seen as a normal part of aging and not a disease. Alzheimer's Disease was generally understood to refer only to the rare, pre-senile

onset dementia. However, a landmark series of cliniconeuropathologic correlation studies first published in the late 1960s (e.g., Blessed et al., Br. J. Psychiatry 114:796-811 (1968)) fundamentally changed the understanding in the art of the nature and prevalence of AD. That work redefined the epidemiology of AD from a rare, presenile dementing disorder to an epidemic disorder responsible for at least 70% of dementia in later life. In 1976, Alzheimer's Disease was described in an influential and widely-cited editorial in the Archives of Neurology as "a *major killer*" and as "[possibly] *the fourth or fifth* most common cause of death in the United States." Katzman, R., "The Prevalence and Malignancy of Alzheimer Disease: A Major Killer," Archives of Neurology, 33: 217-18 (April 1976).

62. Recognition of SDAT as an epidemic disease naturally and understandably produced, with this recognition, an urgent need to find treatments for the disease. In sounding the alarm about the prevalence of Alzheimer's Disease as the true cause of death among the elderly, Dr. Katzman in his editorial did not seek merely to prolong the life of Alzheimer's sufferers, but rather to spur on efforts to treat or prevent the disease. In his words, "[i]n focusing attention on the mortality associated with Alzheimer disease, our goal is not to find a way to prolong the life of severely demented persons, but rather to call attention to our belief that senile as well as presenile forms of Alzheimer are a single disease, a disease whose etiology must be determined, whose course must be aborted, and ultimately a disease to be prevented." (Katzman 1976, page 218).

63. The feeling of urgency in the need for a treatment for AD increased throughout the 1970s and 1980s, as the prevalence of the disease, and its toll on AD sufferers and

their caregivers, became better appreciated, and as the aging of the population increased the number and incidence of AD patients and created a perception of a growing, untreatable epidemic. According to estimates reported by National Institutes of Health's National Institute on Aging in 1986, 2.5 million people were then believed to suffer from AD -- 5 times the estimate of AD sufferers that appeared 10 years earlier. (NIA Report Vol. III 1986, page 2).

64. The epidemic was also understood to impose enormous costs on society. The NIA estimated in 1986 that $35 billion was spent that year on the care of Alzheimer's patients, a figure that included the costs of nursing home and other long-term medical care, but did not account for the incalculable emotional and social costs of the disease. (NIA Report Vol. III 1986, pages 2-3). The Agency also estimated that the cost of special services required by dementia patients was $38 billion, with an additional $39 billion for indirect costs, such as relatives visiting patients in nursing homes, transporting patients for needed medical services, and premature death due to dementia. (NIA Report Vol. III 1986, page 2). Of the costs referenced above, $27 billion reflect "the volume of time spent by relatives who care for Alzheimer patients at home." (NIA Report Vol. III 1986, page 3).

65. The long felt need for AD treatments is reflected as well in the dramatic growth in federal sponsorship of AD research. In 1974, the National Institute on Aging was created with an express mission of conducting and supporting "biomedical, social, and behavioral research and training related to the aging process and the diseases and other special problems and needs of the aged," and Dr. Robert Butler was appointed as the NIA's first permanent Director. (Public Law 93-296, May 31, 1974). In 1977

and 1978, major conferences were sponsored by NIA, NINCDS, and the National Institute on Mental Health (NIMH) to promote and stimulate AD research.

66. In 1979, the Alzheimer's Disease and Related Disorders Association was formed. This organization, which later changed its name to the Alzheimer's Association, became a leading proponent of AD research and efforts to find treatments. In 1984, NIA funded Alzheimer's Disease Centers (ADC) nationwide to conduct research at medical institutions focusing on diagnosis, care, prevention, and treatment of AD.

67. While the need for AD treatments was widely recognized throughout the medical community, by January 1986, almost twenty years after the Blessed articles had reported the AD epidemic, there were still no effective treatments available for AD, especially for the cognitive decline that was the signature feature of the disease.

68. The state of AD treatment at the time is well summed up by Dr. David Drachman, a leading AD researcher at the time who was influential in developing the "cholinergic deficit" hypothesis of AD and who was therefore well-informed on the state of research, particularly as it would have related to cholinergic approaches. He stated in a 1985 publication that "[d]espite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value. It is well to remember that, except for the extraordinary therapeutic success of dopaminergic agonists in Parkinsonism, no other degenerative neurologic disorder has responded to a similar strategy." David A. Drachman, "Treatment of Alzheimer's Disease: New Outlooks for the Future," in C. C. Gottfries, *ed.* Normal Aging, Alzheimer's Disease and Senile Dementia: Aspects

on Etiology, Pathogenesis, Diagnosis and Treatment at 307-308 (editions de l'Université de Bruxelles: 1985).

69. Similarly, Dr. Gene Cohen, a leading geriatric psychiatrist and first Chief of the Center on Aging of the National Institute of Mental Heath, observed in 1983, in discussing efforts to treat the primary symptoms of AD (memory problems and intellectual dysfunction), that "[m]ore than 20 categories of pharmacologic agents have been tried with Alzheimer patients, but no drug has had unequivocal efficacy demonstrated in alleviating cognitive impairment. Questionably positive reports have been debated as reflecting possible placebo effects or accompanying antidepressant action of some of these drugs …." Gene D. Cohen, "Alzheimer's Disease - The Human Concept," in R. Katzman, Banbury Report 15:Biological Aspects of Alzheimer's Disease 3-6, at page 4 (Cold Spring Harbor Laboratory 1983).

70. In short, by January 1986, it had long been recognized that AD was epidemic among the elderly and that no treatments for the disease -- including treatments for the cognitive impairment associated with AD -- yet existed. Development of such treatments was, by that date, a long and pressing need.

VI. SKEPTICISM OF OTHERS

A. The Therapeutic Nihilism Prevailing In The Medical Community

71. Perhaps as a result of this conjunction of long felt need and lack of available treatment, by January 1986 there was considerable skepticism in the medical community about the possibility of a pharmacologic treatment for the cognitive impairment associated with AD.

72. Among treating physicians, this skepticism expressed itself as therapeutic nihilism -- a conviction that the complexities of AD rendered it beyond the reach of pharmacologic treatments entirely. The prevailing view is well captured by a 1985 summary of AD treatment efforts written by Dr. Leo Hollister, a leading pharmacologist on the faculty at Stanford University. Dr. Hollister observes in that publication that "[t]reatment of SDAT is presently far from satisfactory. Many physicians have taken such a negative view of the prospects that they refuse to try anything." L.E. Hollister, "Survey of Treatment Attempts in Senile Dementia of the Alzheimer Type," in C. C. Gottfries, *ed.* Normal Aging, Alzheimer's Disease and Senile Dementia: Aspects on Etiology, Pathogenesis, Diagnosis and Treatment 299-306, at 304 (editions de l'Université de Bruxelles: 1985). Similarly, a review article by Kendall et al. observed the same year that "[m]ost studies on drugs used to treat this disease [AD] are performed badly and tend to show no clinically relevant beneficial effect. The literature makes depressing reading. The doctor tends to regard Alzheimer's as untreatable and all therapeutic agents as useless." M.J. Kendall, et. al., "Therapeutic Progress - Review XVIII Alzheimer's Disease," J. Clin. and Hosp. Pharm., vol. 10, 327-36, at 334 (1985).

B. The Skepticism Among AD Researchers Of A Cholinergic Approach

73. In addition to this therapeutic nihilism prevailing among treating physicians, there was also skepticism among AD researchers of specific pharmacologic approaches, including the cholinergic approach described in the '318 patent.

74. By January 1986, AD was known to be associated with plaques and neurofibrillary tangles and with a wide variety of neurologic symptoms, including memory problems, cognitive dysfunction, and depression. It is also associated with a range of

neurochemical deficiencies, including not only acetylcholine, but also norepinephrine, serotonin, somatostatin, vasopressin, and β-endorphin. The relative importance of these deficiencies was unknown, and there was considerable skepticism among researchers about whether a treatment focused on any one of them, standing alone, would lead to therapeutic improvement. This skepticism was bolstered by the failures of targeted therapies, such as acetylcholine precursor therapy, to show consistent results.

75. A good summary of this skepticism is set forth by Swaab and Fliers, in their 1986 book chapter "Clinical Strategies in the Treatment of Alzheimer's Disease," in Swaab et al., Progress in Brain Research vol. 70 (Elsevier Science 1986). In their introduction, the authors sound a general caution, derived from the long history of failures in the area, about the difficulties of developing a treatment for AD and express skepticism of claims to therapy based on neurochemical logic:

> From the pharmacological literature of the last century it is evident that hypotheses concerning the causal factors of aging and Alzheimer's disease as well as the therapies for treating them were often changing parallel to neurobiological interests and fashions. Clinical strategies were not specific for Alzheimer's disease, but passively followed new developments in medicine and research by trying out nearly every new compound or idea relevant to this condition. This may also explain why therapies that were considered to be 'rational' in the light of a new development, appeared nonsensical as soon as new insights developed....
>
> Repeatedly, ideas about the etiology of Alzheimer's disease have been adapted immediately to new disciplines or insights that developed in neurosciences. Thus changes in hormone levels, blood supply, metabolism, and transmitters have been pinpointed as possible causes of brain aging and Alzheimer's disease. Subsequently, a 'new and promising' therapy was claimed to have a 'rational' basis and was tried out on Alzheimer patients. This history might make us less

> optimistic about all the ongoing clinical trials, and even more convinced about the necessity of fundamental research in Alzheimer's disease before a therapy with a reasonable chance of success will ever succeed in being developed. (page 413)

76. Swaab and Fliers in their review survey the then-current efforts to compensate for the neurochemical deficits associated with AD, including efforts to compensate for the cholinergic deficit in AD with a cholinesterase inhibitor (see page 419), and the authors express considerable skepticism concerning the likelihood of success with any of those efforts:

> There are also some general considerations that make 'neurotransmitter substitution' an enterprise with only a limited chance of success, one of them being the heterogeneous way cells of a given transmitter type change during aging and in Alzheimer's disease.... In addition, deficits have been found in many different transmitter systems in Alzheimer's disease ..., so that normalization of all the different deficits of all the different neurotransmitters throughout the brain would not seem to be a simple task to accomplish.
>
> Apart from the above-mentioned considerations, it is not realistic to expect that one can mimic the complex and naturally occurring spatial-temporal fluctuations of a local transmitter release by means of a global administration of chemical substances. In addition, one can never replace the complete integrating function of a neuron by straightforward administration of transmitter. These are some of the considerations ... which call for skepticism regarding the potentialities of neurotransmitter 'replacement' therapy, whether in the case of neuropeptides or for other putative neurotransmitters. (page 421)

77. The defendants' invalidity contentions suggest that they contend that, by January 1986, the medical community had come to believe that cholinesterase inhibitor therapy would be effective for treatment of the cognitive impairment associated with AD. I disagree. To the contrary, at that time the prevailing view among AD researchers showed considerable skepticism of cholinesterase inhibitor therapy. It

would be almost a decade, until late 1993, that the first cholinesterase inhibitor (tacrine) was approved by FDA for the treatment of AD.

78. As an initial matter, even among those researchers who believed in a cholinergic approach, cholinesterase inhibition would not appear promising, since it was known at the time that cholinesterase levels of AD patients were themselves reduced by the disease, rendering the enzyme an undesirable pharmacologic target.

79. In addition, many researchers were skeptical that cholinesterase inhibition was a viable means for increasing acetylcholine levels, either because blocking cholinesterase would impair the natural breakdown of intra-synaptic acetylcholine into precursor choline which would otherwise then be recycled into synaptic acetylcholine or because the body might respond to the presence of an cholinesterase inhibitor by producing more cholinesterase. Some researchers went ever further, expressing the fear that this inhibition of acetylcholine recycling would in fact spur neuronal destruction through the breakdown of cell membranes. This so-called "autocannabalism hypothesis" was advanced by Richard Wurtman, a leading AD researcher on the faculty of the Massachusetts Institute of Technology, who warned in 1985, for example, that cholinesterase inhibitors "by slowing the hydrolysis of intra-synaptic acetylcholine, diminish the amount of free choline available for re-uptake into the terminal and for acetylation back to acetylcholine; their administration thus risks depleting the terminals of their free choline and accelerating the hydrolysis of membrane phospholipids." R.J. Wurtman, "Activation of Neurotransmitters in the Brain: Strategies in the Treatment of AD/SDAT" in C. C. Gottfries, *ed.* Normal Aging, Alzheimer's Disease and Senile Dementia: Aspects on Etiology, Pathogenesis,

Diagnosis and Treatment 275-280, at 277 (editions de l'Université de Bruxelles: 1985).

80. Wurtman also expressed a skepticism common among researchers at the time that cholinesterase inhibitors simply were not specific enough in their activity to provide safe therapy for AD: "A drug that inhibited acetylcholinesterases everywhere, as physostigmine apparently does, and thus enhanced cholinergic transmission everywhere, would have too many side-effects to be used clinically.... If the acetylcholinesterase enzymes are biologically heterogeneous, such that the acetylcholinesterase present in the vicinity of cortical cholinergic synapses differs from that associated with, for example, vague nerve synapses, then it may be possible to design drugs that affect the former but not the latter enzymes. At present, no such drugs are known." (Wurtman 1985, pages 276-77).

81. In simple terms, the concern stemmed from the fact that acetylcholine is a major nerve transmitter in the neuromuscular system and the heart, as well as in the brain. For this reason, administration of a cholinesterase inhibitor would be expected to impact the functioning not only of the brain (and then, only if it crossed the blood-brain barrier) but also of the neuromuscular system and potentially of the heart. A cholinesterase inhibitor would thus be expected to have multiple side effects and, at best, a narrow therapeutic window. That is, any dose of the drug large enough to produce therapeutic effect in AD might also have such substantial adverse effects as to be intolerable and hence prevent its therapeutic use (as ultimately proved to be the case with metrifonate).

82. Moreover, the AD research published up through January 1986 on cholinesterase inhibitors, mostly involving the cholinesterase inhibitor physostigmine, showed inconsistent and often discouraging results. Zhaven Khachaturian, the founder of the Alzheimer's Association and architect of the federal Alzheimer's Disease Centers' programs, in his testimony before Congress in November 1984, observed that "[d]espite some promising initial results in treatment of Alzheimer disease with agents such as choline, lecithin, and physostigmine, this effort in cholinergic pharmacology has not produced any consistent or long-lasting treatments for Alzheimer disease." (Hearing before the Subcommittee on Aging of the Committee on Labor and Human Resources United States Senate, Nov. 1984, page 55). Similarly, Swaab and Fliers, in their 1986 survey of treatment attempts, concluded that "although 'some clinical improvement can occasionally be seen' …, a satisfactory treatment of Alzheimer's disease by means of pharmacological substitution for deficits in the cholinergic system seems, at present, not to be feasible." (Swaab and Fliers 1986, page 419).

83. Many who were considering cholinergic therapies found the agonist approach more appealing, among other reasons because agonists do not depend for their effect upon a functioning presynaptic cholinergic neuron. In the words of Raymond Bartus, a leading researcher at Lederle Laboratories, and his coauthors, "[c]ertainly drugs requiring functionally intact, presynaptic cholinergic terminals (such as cholinergic precursors and anticholinesterases) should be less capable of improving cholinergic tone or restoring the balance of the central nervous system than are drugs that interact with postsynaptic cholinergic neurons." (Bartus, R., *et al.*, "The Cholinergic

Hypothesis: A Historical Overview, Current Perspective, and Future Directions," in Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives, Annals of the New York Academy of Sciences 1985; 444: 332-58.) Following this logic, various muscarinic agonists, such as arecoline, bethanechol, oxotremorine, pilocarpine, RS 86, and xanomeline were studied in clinical trials. None succeeded. To date, not a single agonist has been approved by FDA as a treatment for AD.

VII. FAILURE OF OTHERS

84. By January 1986, research had been conducted on a wide range of possible therapeutic approaches to the treatment of AD, without success. As indicated above, at that time there was a long felt need for an effective treatment for cognitive decline at the center of the disease, and the many failed attempts to develop such a treatment – both before and after January 1986 – clearly demonstrates, in my opinion, that no particular treatment, or even treatment approach, was obvious at that time.

85. A survey of the treatment approaches that had been tried as of 1986 is set forth in the Swaab and Fliers 1986 book chapter entitled "Clinical Strategies in the Treatment of Alzheimer's disease" discussed above. The authors outline approaches to treatment such as cerebral vasodilators, classical psychotherapeutic drugs, central nervous system stimulants, neurotransmitter substitution therapies, and other miscellaneous therapies.

86. The first category of treatment attempts reviewed by Swaab and Fliers (after a description of historical attempts to treat "senility" or aging through hormonal treatments and the like) are the cerebral vasodilators. (page 416) The use of

vasodilators was based on the (erroneous) assumption that AD was caused by cerebral arteriosclerosis. The authors provide examples of vasodilators that had been tried or suggested by 1986, including carbon dioxide and carbonic anhydrase inhibitors such as acetazolamide; papavaerine; cyclandate; nicotinic acid; and tocopherol (vitamin E). As the authors noted in 1986, many of these lacked any evidence of efficacy. As of today – twenty years later – none has been approved by FDA for the treatment of AD. In addition, as the article notes, researchers had also tried dicumarol, warfarin, and other anticoagulants as treatments under the theory that cerebral emboli (that is, blood clots) might be contributing to the disease. These too have never been approved by FDA.

87. Second, Swaab and Fliers review "classical psychotherapeutic drugs" used to treat Alzheimer's disease, such as antidepressants, neuroleptics, and anxiolytic agents. (pages 416-17) While such agents may be useful to treat certain neuropsychiatric symptoms associated with AD, they do not treat the underlying cognitive decline and, as the authors note, some of the drugs commonly prescribed at the time, such as the benzodiazepines, may in fact worsen the cognitive symptoms.

88. The third category reviewed by the authors is the central nervous system stimulants, which were intended to treat AD based on improvements in brain metabolism. This approach ultimately led to a whole new class of drug compounds – known as "nootropics" – intended as "cognition enhancers." Swaab and Fliers were rightly skeptical of this treatment approach. As they note, claims that piracetam (the first nootropic) enhanced memory and learning were based on "methodologically imperfect studies," whereas "careful studies … did not show any significant effect as

compared to placebo, upon psychometric performance of Alzheimer patients." (page 417)

89. Other CNS stimulants or metabolic enhancers reviewed by the authors, such as magnesium pemoline (Cylert®), yeast RNA, anabolic agents (such as fluoxymesterone and isoprinosine), pentylenetetrazole, methylphenidate, procaine, and nafronyl similarly appear to lack beneficial effect and remain unapproved by FDA for AD treatment.

90. Another interesting example of an attempt to treat AD with a metabolic enhancer discussed by the authors is the drug composed of ergoloid mesylates, which was marketed under the tradename Hydergine®. Initially developed as a vasodilator, Hydergine® was subsequently classified as a "metabolic enhancer" because in some tests it induced a change in cyclic-AMP levels although it is unclear how Hydergine® was thought to affect Alzheimer's disease. Several theories were suggested regarding Hydergine®'s mechanism of action include binding to dopamine, serotonin, and noradrenaline receptors. An alternative mechanism of action is the decreased levels of prolactin associated with Hydergine®. Swaab and Fliers are skeptical of claims to efficacy for Hydergine®, noting that "[t]his clearly illustrates how time after time the commercial machinery gets its hand on whatever neurobiological approach is in fashion at the moment." (page 418). Careful work done by Dr. Troy L. Thompson and others showed Hydergine® to be ineffective in the treatment of AD and possibly even to "cause cognitive dysfunction, perhaps through a direct toxic effect or by accelerating the progression of Alzheimer's disease." Thompson, T. *et al.*, "Lack of

Efficacy of Hydergine in Patients with Alzheimer's Disease," New England J. of Med. 323:445-448 (1990).

91. The fifth category of treatment attempts reviewed by Swaab and Fliers is "neurotransmitter substitution therapies" intended to compensate for deficiencies in various neurotransmitters seen in Alzheimer's patients. The four categories of neurotransmitters discussed by the authors are acetylcholine, monoamines, amino acids, and neuropeptides. As noted above, the authors are quite skeptical of each of these approaches (including the use of a cholinesterase inhibitor to address the cholinergic deficiency) and of the many drugs reviewed by them – including the cholinesterase inhibitor physostigmine; the dopamine agonist bromocriptine; the benzodiazepines (which influence amino acids); and neuropeptides such as vasopressin or ACTH analogs – not one has yet been approved as a treatment for AD.

92. Finally, Swaab and Fliers review various miscellaneous therapies with a wide range of rationales, including nicotinic acid, combinations of Vitamin B-12 and zinc-DL-aspartate, Vitamin E, and chelation therapy related to a perceive link between aluminum levels and AD. None of these approaches has yet proved effective, though hope remains for Vitamin E and related antioxidants.

93. Thus, by 1986, there had been many attempts to develop a treatment for AD, without success. Attempts to treat AD did not stop in 1986, of course, and there have been many failures since. Indeed, I have been involved in a number of such failed attempts, including the clinical trials of acetyl-l-carnitine (Sigma Tau Pharmaceutical Co.); metrifonate (Bayer); and xanomeline (Lilly).

94. Acetyl-l-carnitine ("Alcar") was an agent developed for cognitive enhancement based on the theory that carnitine was a critical element for neuronal metabolism. It was hoped that improving cellular metabolism would help cognition, and hence that Alcar would thus ameliorate the cognitive decline associated with AD. Large scale clinical trials to test the therapeutic benefit of Alcar as an AD treatment were started in early 1990s. I found the logic of Alcar sufficiently persuasive to participate in the clinical trial and hence treat AD patients with this candidate drug therapy. Unfortunately, clinical trials showed no difference between drug and placebo. Indeed, a second large-scale trial was then conducted on younger AD patients, based on an analysis of the first trial that suggested that younger AD patients may have benefited from the therapy, but the second trial too showed no difference between treatment and placebo.

95. Such large pharmaceutical investment in Alcar shows that a cholinesterase inhibitor approach was not the obvious route to cognitive improvement in AD patients and that it was not obvious what therapeutic approach would ultimately succeed.

96. Another example of a failed attempt to develop an AD treatment is Lilly's effort to develop a treatment with the cholinergic agonist xanomeline. The mechanism of xanomeline is to interact directly with the post-synaptic cholinergic neuron. This treatment approach was hypothesized to stimulate post-synaptic function and normalize cognition in the absence of a functional presynaptic cholinergic system. This approach was thought at the time to be more promising than a cholinesterase inhibitor, which depended upon the compromised pre-synaptic system. I found the logic of sufficient interest to participate in the trial, but large-scale clinical trials showed minimal cognitive benefit and substantial side effects. After considerable

effort and investment, the drug was abandoned and has never been approved by FDA for any purpose.

97. A third example is metrifonate, which was a cholinesterase inhibitor pursued by Bayer. Metrifonate is an irreversible cholinesterase inhibitor, and for a long time, was seen by many as the most promising cholinesterase inhibitor candidate. Metrifonate had long been used for the treatment of schistosomiasis. This prior experience gave hope that the drug would prove safe, a hope bolstered by the fact that metrifonate is not metabolized through the liver, a potentially significant difference in AD patients, who may be hepatically impaired. In addition, metrifonate was known to be a potent cholinesterase inhibitor, and the combination of its potency and the fact that it was irreversible suggested that it could be therapeutically administered in small and infrequent doses.

98. The logic underlying metrifonate is set forth in my 1998 publication "Metrifonate: Overview of Safety and Efficacy" in Pharmacotherapy 1998; 18 (2 Pt 2) 43S-46S. Metrifonate is a long lasting, cholinesterase inhibitor that "is spontaneously and nonenzymatically converted to DDVP by dehydrochlorination. Plasma half-lives are approximately 2 hours and 4 hours respectively. Cholinesterase inhibition by DDVP is mediated by a competitive interaction with acetylcholine, followed by dimethyl phosphorylation of a serine residue at the active site of the enzyme. The interaction is stable and long lasting, but can be reversed by oxime. Cholinesterase activity occurs in concert with de novo synthesis of the enzyme (9 days in plasma, 20 days in red blood cells). Thus, prolonged elevation of acetylcholine levels is achieved with metrifonate." (Cummings 1998, pages 43S-44S). Metrifonate inhibits

acetylcholinesterase and butyrylcholinesterase and is completely absorbed and goes through little protein binding. It has no intrinsic anticholinesterase activity. Metrifonate is slowly and nonenzymatically transformed to DDVP, which competitively inhibits acetylcholinesterase, leading to an increase in brain acetylcholinesterase within 1 hour of oral administration. (Cummings 1998, page 44S). Metrifonate was well tolerated and the side effects were predominantly gastrointestinal in nature, and no hepatotoxicity was observed.

99. As this indicates, I was sufficiently taken by the logic of metrifonate to participate in large-scale clinical trials in the mid-1990s. Clinical trials proceeded smoothly until the late stages of drug development, when profound side effects emerged in a few patients. For this reason, further development of the drug was suspended.

100. The metrifonate failure shows that pharmacologic characteristics of a cholinesterase inhibitor that would be both safe and effective for the treatment of AD were unclear, and certainly not obvious. That metrifonate, a leading cholinesterase inhibitor candidate at the time, did not succeed, as well as the many other cholinesterase inhibitors that were taken into clinical trials but not progressed to approval, shows the difficulties in selecting the pharmacologic profile necessary for a cholinesterase inhibitor to treat AD successfully.

101. Many drugs have been considered as candidate therapies but for which no adequate demonstration of efficacy has been made. There have been, of course, many additional failed attempts to develop a treatment for AD. A good survey may be found in a review sponsored by the American Academy of Neurology and the Alzheimer's Association and endorsed by the American Association of Neuroscience

Nurses and the American Geriatrics Society that I published with a number of my colleagues in 2001: Doody, R.S. *et al.*, "Practice Parameter: Management of Dementia (an evidence based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology," Neurology, 56:1154-66 (2001). Among other things, the Subcommittee reviewed the evidence on almost 50 drugs that had been tried as potential treatments for the cognitive decline in AD. The only agents found effective by the Subcommittee were a few cholinesterase inhibitors; for the rest, there was at best "incomplete or conflicting evidence." (page 1157).

102. Another example of the difficulties in developing a treatment for AD is estrogen hormone therapy. In the early to mid 1980s, estrogen treatment was advanced as a cholinergic strategy, on the belief that estrogen (or estradiol) worked at least in part by improving the functioning of cholinergic neurons. Over time, researchers began to believe that estrogen might instead serve as neuro-protective to slow progression of the disease. The Subcommittee's 2001 review found no evidence to support the efficacy of estrogen therapy and made the specific practice recommendation, based on a "high degree of clinical certainty" that "[e]strogen should not be prescribed to treat AD." (page 1158). There is now evidence that estrogen may increase risk of dementia.

103. It is also worth noting that even the vast majority of efforts to find an effective cholinesterase inhibitor failed. For example, of the "first generation" of cholinesterase inhibitors to be tried – physostigmine and THA – only one, tacrine, proved safe and effective. Extensive efforts to develop a physostigmine-based

treatment never succeeded, and even tacrine has proved an undesirable treatment. In a 1997 review titled "Cholinesterase Inhibitors Do More Than Inhibit Cholinesterase," in Giacobini & Becker, eds., Alzheimer Disease: From Molecular Biology to Therapy, 188-204 (1986). Ezio Giacobini – a respected authority on cholinesterase inhibitors – surveyed the history to 1996 of efforts to find cholinesterase inhibitors to treat AD. He lists (in Table III) 16 in clinical trials in 1996. Yet, as of today, only three of these drugs are commonly prescribed – donepezil (Aricept®), approved in the US in 1996; rivastigmine (Exelon®), approved by FDA in 2000; and galantamine (first approved by FDA in 2001 under the trade name Reminyl®). Tacrine (Cognex®) was approved in 1993 but is rarely prescribed because of associated side effects, including possible liver damage. The failed cholinesterase inhibitors tested in clinical trials include:

a. Eptastigmine (also known as heptylphysostigmine) sponsored for trials by Mediolanum.

b. Metrifonate, sponsored by Bayer.

c. Physostigmine SR, the slow release formulation of physostigmine sponsored by Forest.

d. Huperzine A, an herb tested by the Chinese Academy of Sciences.

e. Takeda's TAK-147.

f. Nikken's NIK 247.

g. Pfizer's CP-118,954.

h. Marion Merrel Dow's MDL 73,745.

i. Astra Arcus' NX-066.

j. Hoechst-Roussel's Velnacrine (HP 029 or Mentane).

k. Schwabe's KA-672.

l. Chiesi's GEN 2819.

m. Hoechst-Roussel's Suronacrine (HP128).

104. In my opinion, the fact that so many cholinesterase inhibitors have been tried but failed (and the number reaching clinical trials are of course only a fraction of those subjected to preclinical development such as animal testing) both shows the difficulties of finding a satisfactory cholinesterase inhibitor and rebuts the notion that the characteristics of a cholinesterase inhibitor safe and effective for the treatment of AD were obvious by 1986.

VIII. UNEXPECTED BENEFITS OF GALANTAMINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

105. I believe that galantamine provides benefits in the treatment of AD that were neither known nor expected of a cholinesterase inhibitor in 1986, even among those who pursued a cholinesterase inhibitor strategy for the treatment of AD.

106. The logic behind pursuit of a cholinesterase inhibitor was the relationship between the cholinergic deficit and memory loss. Early studies of cholinesterase inhibitors thus studied whether a cholinesterase inhibitor could reverse the memory and other cognitive deficits of AD. That is, the focus was on memory, language, visual-spatial skills, and praxis.

107. To be clear, it is my opinion that using galantamine to treat Alzheimer's disease was not obvious in 1986. In addition as discussed below, the range and scope of benefits provided by galantamine in treating AD have also been surprising and unexpected.

108. AD is more than just cognitive decline, and it encompasses behavioral and functional abnormalities as well. For example, the vast majority of Alzheimer's patients, even at the mild or moderate stages of the disease, exhibit non-cognitive neuropsychiatric symptoms, including (in decreasing order of incidence): abnormalities of mood (e.g., depression, anxiety, and irritability), apathy, periods of agitation, aberrant motor behavior (e.g., pacing, rummaging, and wandering), disinhibition (that is, socially inappropriate behavior), and elements of psychosis (e.g., delusions and hallucinations).

109. In 1986, it was recognized that AD was associated with both cognitive and non-cognitive abnormalities, though the understanding and measurement of these was still at a rudimentary stage. A leading measure of the abnormalities in AD in January 1986 was the Alzheimer's Disease Assessment Scale, or "ADAS," which included both a cognitive and a non-cognitive portion, referred to respectively as the "ADAS-Cog" and "ADAS-Noncog".

110. A current, widely-used method for measuring the emergence and severity of behavioral abnormalities in Alzheimer's patients is the Neuropsychiatric Inventory ("NPI"), which I developed. The NPI is a validated informant-based interview used in clinical research studies to evaluate neuropsychiatric symptoms and their treatment in dementia patients. See "The Neuropsychiatric Inventory: Comprehensive Assessment of Psychopathology in Dementia" in Neurology 1994; 44:2308-2314. The NPI is an instrument to assess neuropsychiatric symptoms in 10 domains (now 12) by interviewing a caregiver who lives with the patient. It covers the following neuropsychiatric symptom domains: delusions, hallucinations, agitation/aggression,

dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors, and now also nighttime behavioral disturbances, and appetite/eating disturbances. The details of the NPI are described in the following papers: See "The Neuropsychiatric Inventory: Comprehensive Assessment of Psychopathology in Dementia" in Neurology 1994; 44:2308-2314 and "The Neuropsychiatric Inventory: Assessing Psychopathology in Dementia Patients" in Neurology 1997;48:S10-S16.

111. In 1998, my colleague Dr. Kaufer and I added an integrated caregiver measure to the NPI, the Caregiver Distress Scale, to provide a measure of the distress experienced by caregivers of Alzheimer's patients. See "Assessing the Impact of Neuropsychiatric Symptoms in Alzheimer's Disease: The Neuropsyschiatric Inventory Caregiver Distress Scale." I have also developed an assessment scale based on the NPI for use in nursing homes: the NPI-NH.

112. As I will discuss below, galantamine has been shown to have a beneficial effect on the behavioral abnormalities associated with AD as measured by the NPI. It has also been shown to reduce caregiver distress as measured by the caregiver distress scale of the NPI. Neither of these benefits would have been known or expected of galantamine, or any cholinesterase inhibitors, in January 1986.

113. As an initial matter, as of 1986, cholinesterase inhibitors had not been associated with the treatment of behavioral abnormalities. Initially developed as nerve gases and insecticides, the accepted therapeutic uses of cholinesterase inhibitors in 1986 were quite limited. For example, the Merck Manual at the time described reversible cholinesterase inhibitors as "primarily used as miotics in ophthalmology and in

treating myasthenia gravis and anticholinergic drug poisoning" and irreversible cholinesterase inhibitor as "therapeutically useful only as long-acting miotics in treating certain types of glaucoma." The Merck Manual of Diagnosis and Therapy, pp. 2353, 2354 (14th ed. 1982).

114. At most, the connection between cholinesterase inhibitors and cognition was through an analogy based on its role in reversing anticholinergic drug poisoning. There was no connection drawn between cholinesterase inhibitors and the treatment of behavioral abnormalities.

115. A number of early studies found that cholinesterase inhibitors did not improve non-cognitive symptoms as measured by the ADAS non-cog scale. (M. Farlow *et. al*, for the Tacrine Study Group. A controlled trial of Tacrine in Alzheimer's disease. JAMA 1992; 268:2523-2529; M. Knapp, *et. al* for the Tacrine Study Group. A 30-week randomized controlled trial of high-dose Tacrine in patients with Alzheimer's disease. JAMA 1994;271:985-991; K. Davis, et. al. A double-blind, placebo-controlled multicenter study of Tacrine for Alzheimer's disease. N. Engl J. Med. 1992; 327-1253-1259.). Moreover, when the effect of cholinesterase inhibitors on behavioral abnormalities in AD was studied in the late 1980s, the results were negative. (Farlow 1992, Knapp 1994, Davis 1992).

116. Unexpectedly, however, it has turned out that galantamine does have a beneficial effect on the behavioral abnormalities in AD. In 2004, I published an article, "Reduction of Behavioral Disturbances and Caregiver Distress by Galantamine in Patients with Alzheimer's Disease," in Am J Psychiatry 2004; 161:532-538. Neuropsychiatric symptoms were measured using the NPI in four different groups:

placebo, patients taking 8 mg of galantamine per day, patients taking 16 mg of galantamine per day, and patients taking 24 mg of galantamine per day. As described in more detail in the paper, we found that galantamine therapy was associated with reduced emergence of behavioral disturbances and improvement in existing behavioral problems in patients with mild to moderate AD, with a concomitant reduction in reported caregiver distress.

117. The mechanism by which galantamine improves the behavioral abnormalities associated with AD is not entirely clear. There are multiple mechanisms by which galantamine could be hypothesized to have a psychotropic effect. First, the acetylcholine deficiency of AD is marked in the limbic system, and enhancement of limbic function with a cholinesterase inhibitor may ameliorate behavioral abnormalities. The part of the limbic system associated with memory is different than that associated with behavior, and hence (as of 1986) use of a cholinesterase inhibitor to improve memory or cognition would not be expected to also improve behavior.

118. Second, the allosteric nicotinic modulation exerted by galantamine increases arousal and may decrease aberrant motor behavior and agitation, similar to the effects of psychostimulants in improving symptoms of hyperactivity in children with attention deficit disorders. Galantamine's allosteric modulatory effect was not known in 1986; nor at that time was there any connection drawn between nicotinic stimulation and improvement in aberrant motor behavior or agitation.

119. Third, improved function of nicotinic thalamofrontal projections may reduce agitation, disinhibition, and apathy, which appear to be frontally mediated. Again, this was entirely unknown in 1986.

120. Fourth, galantamine has secondary effects on other transmitters, and these subsequent events may be partially responsible for the psychotropic effects of the agents. This too was not known or expected in 1986.

121. It is also worth noting that the improvements in behavior following treatment with galantamine are largely independent of the cognitive improvements. As we observed in our paper reporting these improvements, "[t]he absence of correlations between cognitive and behavioral changes following treatment with galantamine indicates that these two domains are independent response dimensions." (page 537) In other words, the behavioral improvements are not simply a result of cognitive improvement, but instead reflect a separate and distinct benefit of galantamine in treating AD.

122. My colleagues and I have recently supplemented our understanding of the therapeutic action of galantamine by conducting a positron emission tomographic ("PET") study of 19 patients with mild to moderate Alzheimer's disease. (Michael Mega, et. al, "Metabolic Patterns Associated with the Clinical Response to Galantamine Therapy: A Fludeoxyglucose F18 Positron Emission Tomographic Study," Arch Neurol. 2005; 62:721-728.) Our purpose was to explore the general metabolic effect of galantamine, which we describe as "a relatively weak cholinesterase inhibitor but a potent nicotinic receptor modulator," and to map the functional patterns associated with cognitive and behavioral responses to galantamine. (p. 722) Although I refer to the paper for a detailed description of our results, we noted the presence of "robust findings support a role for the activation of a relatively normal thalamus in patients responding, either cognitively or behaviorally, to galantamine treatment, and suggest a modulatory role for galantamine on the

nicotinic receptors that have their highest concentration in the thalamus ...." (p. 726) The PET study is suggestive of the potentially complex mechanisms by which galantamine (and perhaps the other approved cholinesterase inhibitors) affect the cognitive and behavioral *symptoms* of AD, *mechanisms* never contemplated or expected in 1986, when the application for the '318 patent was first filed.

123. Another benefit that has observed in the use of galantamine to treat AD is improvement in behavior-related caregiver distress. In the placebo-controlled study discussed above, we also observed a significant improvement in behavior-related caregiver distress for caregivers of those individuals on galantamine therapy." As we noted in the article, "[r]eduction in caregiver distress is an important outcome in treatment of patients with Alzheimer's disease, because caregiver stress and burdens lead to caregiver illness and may precipitate institutionalization of patients with Alzheimer's disease." (Cummings 2004 at 537)

124. The improvements we observed would not have resulted from improved cognition in the patient, but rather from the behavioral improvements observed. The principal cause of caregiver distress is related to behavioral abnormalities rather than cognitive impairment, and it is these behavioral abnormalities (and the resultant caregiver distress) that most frequently precipitates institutionalization. The improvement of caregiver distress seen for galantamine was not known or expected from its cognitive benefits alone, and certainly would not have been known or expected in 1986.

7/28/06
Date

Dr. Jeffrey L Cummings

EXHIBIT A

May 9, 2006

CURRICULUM VITAE

JEFFREY L. CUMMINGS, M.D.

Table of Contents

CURRICULUM VITAE

NAME:	**JEFFREY L. CUMMINGS, M.D.**
TITLE:	The Augustus S. Rose Professor of Neurology Professor of Psychiatry and Biobehavioral Sciences Director, UCLA Alzheimer's Disease Center Director, Deane F. Johnson Center for Neurotherapeutics Executive Vice Chair, Department of Neurology David Geffen School of Medicine at UCLA
ADDRESS:	Department of Neurology University of California, Los Angeles 710 Westwood Plaza, Suite 2-238 Los Angeles, CA 90095-1769
DATE OF BIRTH:	March 8, 1948
PLACE OF BIRTH:	Basin, Wyoming
CITIZENSHIP:	United States

EDUCATION:

Baccalaureate	University of Wyoming, graduation with High Honors, Bachelor of Science (Zoology), 1966-1970.
Doctorate	University of Washington School of Medicine, Seattle, Washington, M.D., 1970-1974.
Internship	Flexible Internship, Hartford Hospital, Hartford, Connecticut, 1974-1975.
Residency	Neurology, Boston University School of Medicine, Boston, Massachusetts, 1975-1978.
Fellowship I	Behavioral Neurology, Boston University School of Medicine, Boston, Massachusetts, 1978-1979.
Fellowship II	Postgraduate studies in Neuropathology and Neuropsychiatry, Institute of Neurology National Hospital for Neurological Diseases Queen Square, London, England, 1980.

PROFESSIONAL EXPERIENCE:

	Boston University School of Medicine
1978 - 1979	Chief Resident in Neurology, Instructor in Neurology, Boston University School of Medicine.
	Instructor, *Clinical Medicine (Neurology), Laboure Junior College, Boston, Massachusetts.*
1979 - 1980	Director of Behavioral Neurology, Boston University Medical Center; Assistant Professor of Neurology, Boston University School of Medicine.
	Consultant in Neurology, VAMC Boston.
	Physician Coordinator, Wald Neurological Unit, Boston University Medical Center.
	Department of Veterans Affairs
1981 - 1988	Chief of Medicine, West Los Angeles VAMC (Brentwood Division).
1984 - 1988	Assistant Clinical Director, Nursing Home Care Unit, West Los Angeles VAMC.
1989 - 1996	Associate Chief of Psychiatry for Neurobehavior, West Los Angeles, VAMC.
1980 - 1990	Director, Neurobehavior Unit, West Los Angeles VAMC (Brentwood Division).
1986 - 1991	Co-Chief, Movement Disorders Laboratories, West Los Angeles VAMC (Brentwood Division).
1992 - 1997	Director, VA Geriatric Neurology Fellowship, West Los Angeles VAMC.
1996 - 1999	Consultant to the Neurobehavior Unit, Psychiatry Service, West Los Angeles VAMC.
	UCLA School of Medicine
1980 - 1986	Assistant Professor of Neurology in Residence, UCLA School of Medicine.
1985 - 1991	Clinical Co-Director, Alzheimer's Disease and Memory Disorders Clinic, UCLA School of Medicine.
1986 - 1992	Associate Professor of Neurology in Residence, UCLA School of Medicine.
1986 - 1992	Associate Professor of Psychiatry & Biobehavioral Sciences in Residence, UCLA School of Medicine.
1988 - 1991	Director, Dementia Research Program, UCLA School of Medicine.
1983 - 1994	Co-Director, UCLA Neurobehavior Training Program, Department of Neurology, UCLA School of Medicine.
1991 - 1996	Director, UCLA Geriatric Behavioral Neurology Clinic.
1991 - Present	Director, UCLA Alzheimer's Disease Center.
1992 - Present	Professor of Neurology and of Psychiatry & Biobehavioral Sciences, UCLA School of Medicine.
1994 - Present	Director, UCLA Dementia and Neurobehavior Research Fellowship
1996 - Present	*The Augustus S. Rose Professor of Neurology (endowed chair)*
2000 - 2001	Vice Chair, Department of Neurology
2002 - Present	Executive Vice Chair, Department of Neurology
2003 - Present	Director, Deane F. Johnson Center for Neurotherapeutics at UCLA

CERTIFICATION:

1975	National Board of Medical Examiners
1979	American Board of Neurology and Psychiatry (Neurology)

MEDICAL LICENSURE:

1978	Massachusetts
1980 - Present	California

HONORS AND AWARDS:

1970	Phi Beta Kappa
1973	Epilepsy Foundation of American Student Fellowship; Epilepsy Clinic, University of Washington School of Medicine, AA Ward and JR Green, preceptors.
1974	Thesis Award, University of Washington School of Medicine.
1989	Arthur Cherkin Award (for contributions to Geriatrics and Gerontology at UCLA).
1990	Neurology Faculty Teaching Award; UCLA Department of Neurology.
1992	Research Award, Los Angeles Chapter, Alzheimer's Association.
1993	Psychiatry Senior Faculty Teaching Award; UCLA Department of Psychiatry.
1993, 2001	Best Doctors in America (Neuropsychiatry Section).
1993	Irving and Helga Cooper Award for Geriatrics Research.

1996	Best Doctors in America (Neurology Section).
1996	NorAge - Pharmacia & Upjohn Award for paper "Frequency of dementia in Parkinson's disease" by D. Aarsland, E. Tandberg, JP Larsen, JL Cummings.
1996	The Augustus S. Rose Professor of Neurology; endowed chair
1997	Honorary Member of the American Association of Geriatric Psychiatry
1999	Gold Hugo award for Video *Communicating the Impact of Alzheimer's Disease to Patients and Caregivers*
2000	"Cotzias Lecturer", Spanish Neurological Society
2000	Honoree, Alzheimer Association of Orange County
2002	Elected to American College of Neuropsychopharmacology
2003	23rd Srinivasan Orator; Chennai, India (with medal).
2005	Henderson Lectureship American Geriatric Society (Annual Meeting)
2005	Outstanding Alumni, University of Wyoming

*Invited named lectureships listed at end of CV

SOCIETIES AND AFFILIATIONS:

American Neurological Association

1992 - Present	Member

American Academy of Neurology

1980 - Present	Member
2001 - Present	Fellow
1989 - 1990	Course Director, American Academy of Neurology Neuropsychiatric aspects of Neurologic Disease
1990 - 1992	Member, American Academy of Neurology Self-Assessment for Neurologists Committee Behavioral Neurology Section
1991 - 1993	Member, Subcommittee on Syllabus preparation for Recertification (Behavioral Neurology)
1993 - 1995	Facilitator, panel on Neuropsychology in Neurology; subcommittee of Therapeutics and Technology Assessment Committee
1993	Abstract Review Committee, Behavioral Neurology and Neuropsychiatry Sections
1994 - 1995	Abstract Review Committee, Neuropsychiatric Section
1995 - 1998	Abstract Review Committee, Aging and Geriatric Neurology
1980 - Present	Member, Behavioral Neurology Section
1994 - 1996	President, Behavioral Neurology Section
1998 - 2000	Co-Chair, Panels on Dementia Recognition, Diagnosis and Treatment Guidelines
2002	Abstract Review Committee, Session Co-Chair, Behavioral Neurology Section
2003	Co-Chair, Dementia Platform Abstract Session
2003 – Present	Course Director, Non-Alzheimer Dementias
2004	Chair, Abstract Review Committee, Behavioral Neurology

International Neuropsychological Society

1985 – Present	Member

Behavioral Neurology Society

1986 – Present	Member
1992 - 1994	Counselor
1992 - 1997	Chair, Certification and Accreditation Committee
1994 – 1996	President

American Psychiatric Association

1983 – Present	Member

Society of Biological Psychiatry

1985 – Present	Member

American Geriatric Society

1993 – Present	Member
1993	Abstract Review Committee

Movement Disorders Society
1987 – 2000 Member

American Neuropsychiatric Association
1990 – Present Member
1993 – Present Member Research Committee
1993 – 1996 Board of Directors
1996 Executive Director
1996 – 1998 Abstract reviewer
2000 Fellow

UCLA Brain Research Institute
1993 - Present Member

American Association for the Advancement of Science
1988 - Present Member

Society for Neuroscience
1993 - 2000 Member

American Medical Association
1997 - Present Member

Collegium Internationale Neuropsychopharmacologium
1998 - Present Member

American Association of Geriatric Psychiatry
1998 - Present Member (honorary)

Neuropsychiatric Institute, UCLA
(Peter Whybrow, Director)
1998 - Present Senior Research Scientist

Institute of Brain Aging and Dementia, UCI
(Carl Cotman, Director)
2000 - Present Member

Institute for Neurodegenerative Disease, UCSF
(Stanley Prusiner, Director)
2000 - Present Member

International College of Geriatric Psychoneuropharmacology
2000 - Present Founding Member

International Psychogeriatric Association
2000 - Present Member

American College of Neuropsychopharmacology
2002 - Present Member (Limited elected membership)

American Society for Experimental Neurotherapeutics (ASENT)
2001 - Present Member

Egyptian Neurological Society
2000 - Present Honorary Member

Thai Neurological Society
2004 - Present Honorary Fellow

COMMITTEES AND SERVICES:

	Department of Veterans Affairs
1982 - 1987	Research and Development Committee West Los Angeles VAMC (Brentwood Division)
1981 - 1983	Medical Records Committee West Los Angeles VAMC (Brentwood Division)
1982 - 1986	Therapeutic Agents and Pharmacy Committee West Los Angeles VAMC (Brentwood Division)
1983 - 1989	Director's Task Force for Development of VAMC West Los Angeles Nursing Home Care Unit
1981 - 1988	Member, GRECC Advisory Committee West Los Angeles VAMC
1984 - 1988	Mental Health Council, West Los Angeles VAMC (Chairman, 1988)
1987 - 1988	Chairman, Residency Commission West Los Angeles VAMC (Brentwood Division)
1989 - 1999	Member, Dean's Committee West Los Angeles VAMC
1993 - 1997	Chair, GRECC Advisory Committee, West Los Angeles VAMC
1995 - 1996	Member VACO Office of Geriatrics and Extended Care Dementia Workgroup
	UCLA School of Medicine
1983 - 1990	Assistant Chief of Neurology, Neuropsychogeriatrics Division of Department of Psychiatry UCLA School of Medicine
1985 - 1986	Member, Geropsychiatry Cluster Planning Committee, Rural Affiliated Neuropsychiatric Cluster Hospital (RANCH), UCLA
1988 - 1990	Chairman, Priority 5 Committee UCLA Department of Neurology
1989 - Present	Member, Residency Selection Committee UCLA Department of Neurology
1989 - 1991	Neuroscience Curriculum Work Group UCLA
1990 - 1992	Chairman, Medical Student Education Committee Department of Neurology, UCLA
1990 - 2000	Chairman, Thesis Committee Department of Neurology, UCLA
1990 - 1993	Member, Quality Assurance and Peer Review Committee, Department of Neurology, UCLA
1990 - 1993	Faculty Planning Committee Center for Aging, UCLA
1985 - Present	Academic Geriatric Resource Center Committee UCLA School of Medicine, Member
1992 - 1999	Member, Geriatric Medicine Intensive Course Steering Committee
1993 - 1994	NPI Director's Policies and Resources Advisory Committee
1993 - 1996	Member, UCLA Faculty Executive Committee
1994 - 1995	Chair, UCLA Neurology Search Committee (4 Neuroscience Positions)
1995	Member, UCLA Chair of Psychiatry Search Committee
1995 - Present	Member, Department of Neurology Promotions Committee
1996	Member, UCLA Center on Aging Director Search Committee
1997 - Present	Brain Research Institute Steering Committee
1997	Member, UCLA 5-Year Review Committee (Department of Molecular and Medical Pharmacology)
1997	Brain Research Institute Review Committee (Chair 2000-2003)
2000 - Present	Chair, Department of Neurology Promotions Committee
2000 - Present	Member, Scientific Advisory Board, Center for Vulnerable Populations Research
	Miscellaneous
1986 - 1990	Scientific Advisory Board Los Angeles Resource Center (For Adults with Brain Impairment and their Caregivers)
1983 - 1990	Neurological Consultant, Los Angeles Chapter Tourette Syndrome Association
1991 - 1995	Consultant, American Medical Association Drug Evaluations Text and Periodicals
1992 - 1993	Member, Sigma Tau Scientific Journalism Award (to judge and reward outstanding journalism concerning Alzheimer's disease)
1990 - 1992	Consultant, California Athletic Commission
2000 - Present	Member, Scientific Advisory Board, Institute for the Study of Aging
2004 – Present	Alzheimer's Research Forum Board

NATIONAL AND INTERNATIONAL GOVERNMENTAL SERVICES:

Neurological Consultant and Lecturer for the Philippine Government (March, 1983).
Invited participant, NINDS-AIREN Workshop on Vascular Dementia. Criteria for diagnosis developed (April, 1991).
Member, NIMH Task Force on the Neuropsychological Assessment of HIV encephalopathy (Nelson Butters, Chairman).
Member, NIMH Work Group on Depression in the Elderly (George Nederhe, Chairman).
NIH Study Section Member (Human Development and Aging; HUD-2), 1988-1992.

National Institute's Health Reviewers Reserve (7/1/92 - 6/30/96).
Reviewer, Medical Research Council of Canada (1989 - 1999).
Consultant, DSM IV Cognitive Impairment Section. (1991 - 1994).
NIA ad hoc Alzheimer's Disease Center reviewer (1994, 2000).
Chair, NIA ad hoc Alzheimer's Disease Center reviewer (2000, 2001).
NIMH ad hoc Geriatric Psychiatry Center review (1996).
Aging and Neuroscience Research in the VA. Presentation to Congress Members and Congressional Staff (1995).
Reviewer, Canadian Alzheimer Association (1992 - present).
Member, Scientific Advisory Board, Sophie and Abram Stuchynski Alzheimer Research and Treatment Center Ramat Gan, Israel (1999 - Present).
NIA, Special Review Panel (for ADRC's), Chair (1999).
Member, NIMH Work group on degeneration in Alzheimer's disease (2002)
Member, NINDS Data Safety and Monitory Board, Depression in Parkinson's disease (2004 – Present)
Chair, NIA Review Committee of Pilot Studies of Treatment for Alzheimer's disease (2002 – Present)
Chair, Alzheimer's Disease Center Ad Hoc Review Committee (2004)
Chair, NIA Review Committee for Alzheimer's Disease Research Center (2004)
Member, NINDS Parkinson Disease Neuroprotective Therapy (NET-PD) Program Advisory Board (2005)
Member, NINDS Treatment of Depression in Parkinson's Disease (SAD-PD) DSMB (2004-2006)

INTERNATIONAL POSITIONS:

Advisor, Alzheimer's Disease Clinic, Jakarta, Indonesia (2000 - Present), (Buku Peringutan Hut RS Dharma Tava ke 29).

ALZHEIMER'S DISEASE CENTER DIRECTORS GROUP:

Member, Steering Committee (1999 - 2000).
Chair, Steering Committee (2001).
Member, National Alzheimer's Coordinating Center Steering Committee (2000, 2001).
Member, Uniform Data Set Task Force (2001-2004)

ALZHEIMER'S ASSOCIATION:

1983 - present	Member, Los Angeles Chapter Alzheimer's Association Scientific Advisory Board
1997 - 2001	Chair, Los Angeles Chapter Alzheimer's Association Scientific Advisory Board
1997 - 2001	Research and Practice Advisory Board, National Alzheimer's Association
1998 - 2002	National Medical and Scientific Advisory Council
1998 - 2002	National Board of Directors
2000 - present	Board Member, LA Chapter
2001 - 2004	President, Board of Directors, LA Chapter

INTERNATIONAL ADVISORY BOARD:

Alzheimer's International – 2005 Meeting (Istanbul, Turkey)
International Neuropsychiatric Association – 2006 Meeting (Sydney, Australia)

NEUROBEHAVIOR AND DEMENTIA FELLOWS:

1980	Ralph Lilly
1982	Michael Frankel
1982	Sandra Horowitz
1984	Steven Read (with Geriatric Psychiatry)
1985	Mario Mendez
1985	Bruce Miller
1986	Jeffrey Davis
1987	Michael Mahler (with Geriatric Medicine)
1987	William Reichmann

1988 Stephen Signer
1988 Adam Darkins
1988 Artiss Powell
1988 Fred Flynn
1988 Jeffrey Victoroff
1989 David Sultzer
1989 Donald Freidenberg
1989 Keith McDaniel
1989 Webb Ross
1990 Greg Gorman
1990 John Absher
1991 Mace Beckson
1991 Douglas Scharre
1992 Michael Mega
1992 Dan Kaufer
1993 Ann Craig
1994 Kevin Gray (with Geriatric Psychiatry)
1994 Katherine White
1995 Mark Wright
1996 Morgan Levy (with Geriatric Psychiatry)
1996 Donna Masterman
1996 Tomo Nakawatase
1996 Terri Edwards-Lee
1996 Tiffany Chow
1997 Seth Weingarten
1997 John Ringman
1997 Barry Jordan
1997 Adrian Mirea
1998 Yuri Bronstein
1998 Julia Chung
1998 Verna Porter (with Geriatric Medicine)
1999 Sylvia Askin-Edgar
1999 Mark Pippenger
2000 Susan Guy
2001 Susan O'Connor
2001 David Clark
2002 Margaret Swanberg
2002 Zakiya Wynn
2003 Liana Apostolova
2004 Gad Marshall
2005 Edmond Teng

INTERNATIONAL SCHOLARS:

1988 Judith Aharon- Peretz (Israel)
1989 Larry Dian (Canada)
1992 C. K. Liu (Taiwan)
1995 Dag Aarsland (Norway)
1996 Dean Foti (Canada)
1997 Ziad Nasreddine (Canada)
1998 Sibel Tekin (Turkey)
1999 Nobuto Hirono (Japan)
2000 Lyna S. Kiemas (Indonesia)
2000 Silvia Lumempouw (Indonesia)
2000 F. C. Pang (Hong Kong)
2000 J-L Fuh (Taiwan)
2000 Cecile Henquet (Netherlands)
2001 Vorapun Senanarong (Thailand)
2002 TJ Hwang (Taiwan)

2002 Fred Assal (Switzerland)
2003 Il-Seon Shin (South Korea)
2003 Mei-Sian Chong (Singapore)
2004 Solasinee Hemrungrojn (Thailand)
2004 Darwin Dasig (Phillipines)
2005 Tuty Yeo (Indonesia)
2005 Encarnita Raya Ampil (Phillippines)
2005 Raphael M. Bonelli (Austria)

Ph.D. DISSERTATION COMMITTEES:

1989 Rena Matteson, UCLA Department of Psychology
1991 Karen Jensen, UCLA School of Nursing
1995 *Patti Lee, Modeling caregiver stress.* UCLA School of Nursing.
1997 Lise Abrams, Aging, orthographic overlap, and implicit versus explicit word retrieval. UCLADepartment of Psychology
1997 Jill Shapira, Patient agitation in one surgical intensive care unit: cultural models of nurse caregiver. UCLA Department of Anthropology.

1997 Michael Mega, Histological in vivo imaging and behavioral correlates in Alzheimer's disease. UCLA Department of Neurosciences
2003 Allison Breggon, Prodromal changes in subjects of genitive siste for Alzheimer's disease; Brain Imaging Center, UCLA Neurosciences.
2004 Shebnam Shadenam, Linguistic change in Alzheimer's disease and Parkinson's disease.
2004 Christina Fales, Executive dysfunction in Parkinson's disease; UCLA Department or Psychology

FOUNDATIONS

John Douglas French Research Foundation
1995 – present Vice Chair, Scientific Advisory Committee

Deane F. Johnson Foundation for Alzheimer's Research
1999 - present Medical Director

Sidell Kagan Foundation
2001 - present Member, Board of Directors

John Douglas French Foundation for Alzheimer's Research
1996 - present Vice Chair, International Scientific Advisory Board
1990 - present Member, Scientific Advisory Board

Tichi Wilkerson Kassel Parkinson's Foundation
2003 – present Medical Director

JOURNAL AND TEXTBOOK SERVICES:

CHAIR, EDITORIAL BOARD: Alzheimer's Disease Management Today (1998 - 1999)

ASSOCIATE EDITOR:
Yearbook of Geriatrics and Gerontology (1986 - 1991)
Brain and Cognition (1986 - 1998)
Journal of Neuropsychiatry and Clinical Neuroscience (1987 - Present)
Psychosomatics (1988 - 2004)
Current Psychiatry Report; editor for Neuropsychiatry (1999 - 2000)

EDITORIAL BOARD:
Alzheimer's Disease and Associated Disorders (1988 - Present)
American Journal of Alzheimer's Disease (2004 – Present)
Archivos de Neurociencias (1998 - Present)

Behavioral Neurology (1987 - 2000)
Caring for the Ages (2000 - Present)
Clinical Geriatrics (1999 - 2002)
Clinical Neurology and Neurosurgery (2005 – Present))
CNS Spectrums (1998 - Present)
Cognitive and Behavioral Neurology (2003 – Present)
Cognitive Sciences (2004)
Current Psychiatry Report (2000 - 2004)
Dementia and Geriatric Cognitive Disorders (2002 - Present)
Demenze (1998 - Present)
Health in Mind and Body (1995 - 1998)
Internal Medicine Thailand (2002 – Present)
International Journal of Neuropsychopharmacology (1998 -2003)
Journal of the American Geriatric Society (1992 - 1997)
Journal of the American Medical Directors Association (2001 - 2004)
Journal of Geriatric Psychiatry and Neurology (1990 - Present)
Long-Term Care Forum (1999 - Present)
Middle-Eastern Journal of Age and Aging (2003 – Present)
Middle-Eastern Journal of Family Medicine (2003 – Present)
Neurocase (1997 - 2003)
Neurology (1992 - 2003)
*Neuropsychiatric Disease and Treatment (2004)
Neuropsychiatry, Neuropsychology and Behavioral Neurology (1987 - 2003)
Neuropsychology (1996)
Neuropsychiatric Disease and Treatment (2004 – Present)
Practical Neurology (2001 – Present)
Psychiatric Times (1992 - Present)
Psychogeriatrics (2000 - Present)
Research and Practice in Alzheimer's Disease (2005)
Textbook of Neuropsychiatry, 2nd Edition (1992), 3rd Edition (1997)
Trends in Evidence-Based Neuropsychiatry (2001 - Present)
The Economics of Neuroscience (1999 – 2001)

* Honorary Editor Board

ADVISORY BOARD:

Neuropsychiatry and Psychopharmacology Raven Press (1989 - 1993)
Mental Fitness (1997 - 1999)
Recent Patents on CNS Drug Discovery (2005)

GUEST EDITOR:

•Special Issue on Psychosis in Neurologic Disease. Neuropsychiatry Neuropsychol Behav Neurol (1991).

•Special Issue on Lewy Body Disease and Related Disorders. Brain Cogn (1995).

•Special Issue on Alzheimer's Disease Therapy. Behavior as an efficacy Outcome. Alzheimer Dis Assoc Disord 11 (suppl 4) (1997).

•Special Issues on Current Perspectives in Alzheimer's Disease. Neurology 51 (suppl 1) (1998).

•Special Issue of J Neuropsychiatry Clin Neurosci (1997).
Salloway S, Malloy P, Cummings, JL, eds.

•Rabins P, Cummings J, eds. Supplement to Am J Geriatr Psychiatry. Alzheimer's disease management; the emerging standard of care. Based on the Proceedings of the Consensus Conference on Alzheimer's Disease and Related Disorders (1997), and the AAGP 10th Annual Meeting (1997).

•Special Issue on Alzheimer's Disease. Primary Psychiatry 6:45 (April 1999).

•Special Report: Practical Alzheimer's Disease Management: A comparative review of new compounds, diagnosis, treatment, and outcomes assessment. Postgrad Med pp. 5-6 (May 1999).

•Special Issue on Alzheimer's Disease. Int J Neuropsychopharmacol (2000).

•Special Section: Treatment of behavioral disturbances In Alzheimer's disease. Dementia Geriatr Cog Providers (2003).

•Supplement Editor: Galantamine Treatment of Alzheimer's disease in long-term care. J Am Med Directors Assoc. (2003)

•Special issue: Parkinson's disease and dementia with Lewy bodies; J Geriatr Psychiatry Neurology (2004 with Dag Aarsland, M.D.)

- Pathogenetic implications and clinical guidelines for the treatment of Alzheimer's disease. Drugs & Aging 2005; 22: S1-40.

SECTION EDITOR:

Comprehensive Textbook of Psychiatry, 6th Edition. Kaplan, Sadock B (eds). Section - Neuropsychiatry (l994).

Current Psychiatry Reports: Neuropsychiatric Disorders (1999).

Current Psychiatry Reports: Neuropsychiatric Disorders (October 2000).

JOURNAL REFEREE:

*Alzheimer's Disease and Associated Disorders
*American Journal of Psychiatry
*American Journal of Geriatric Psychiatry
*Annals of Neurology
*Archives of Neurology
Archives of General Psychiatry
Biological Psychiatry
General Hospital Psychiatry
International Psychogeriatrics
Journal of Clinical Psychiatry
Journal of Geriatric Psychiatry and Neurology
Journal of the International Neuropsychological Society
Journal of Neurology, Neurosurgery and Psychiatry
Journal of the American Geriatrics Society
Journal of the American Medical Association
Journal of Neuroscience
Lancet
Movement Disorders
NeuroImage
*Neurology
Neuron
Neuropsychiatry, Neuropsychology, and Behavioral Neurology
New England Journal of Medicine
Science
Stroke

*Regular reviewer

COLUMNIST:

Psychiatric Times (Brain and Behavior column appears 4-6 times/year) (1988 - 1996; occasional contributor 1996 - present)

PROPOSAL REVIEW SERVICES:
Department of Veteran's Affairs (1992 - 1996)
Medical Research Council of Canada (1992 - present)
Wellcome Foundation, London, England (1993 - present)
National Institute of Health Review Group (1989 - 1993)
National Institute of Aging Ad Hoc Review Committee (1992 - 1994)
National Institute on Aging Special Review Panel, Chair (1999, 2004)
French Foundation for Alzheimer Research (1990 - present)
Alzheimer's Association (1996 - 2003)
Alzheimer Society of Canada (1997 - present)
Swiss National Science Foundation (1998 - 2002)
National Institute on Aging, Pilot Clinical Trials Review Committee, Chair (2002 – present)
National Institute on Aging. Alzheimer's Disease Research Center Ad Hoc Review Chair (2004)

FUNDED RESEARCH:

Obsessions and Compulsions in Tourette Syndrome	Funded by Gatepost Foundation and Tourette Syndrome Association M Frankel, JL Cummings, and DF Benson; 1982 ($18,000).
Alzheimer's Disease	Grant from the LA Alzheimer's Association JL Cummings and DF Benson; 1985 ($1,000).
MRI and PET Studies in Schizophrenia and Dementia	Veterans Administration Grant S Marder, B Oldendorf, JL Cummings, W Blahd, HC Padgett, and MA Mandelkern 1985 ($15,000) for this subproject; (Project total was $75,000 plus MRI purchase and installation).
Language Changes in Alzheimer's Disease	John Douglas French Foundation, JL Cummings, PI; 1985 - 1987 ($30,000).
Intraventricular Bethanechol in Dementia of the Alzheimer	SL Read (PI), JL Cummings, and JG Frazee Funded by the John Douglas French Foundation; 1985 ($30,000).
Speech and Language Alterations in the Dementias	JL Cummings (PI), DF Benson, and MA Hill Funded by the John Douglas French Foundation; 1985 ($30,000).
Alzheimer's Disease: Insight into CNS Mediation of Language	JL Cummings (PI) and D Van Lancker Southern California Alzheimer's Disease Consortium;1987 ($6,000).
Neurological Imaging in Multi-Infarct Dementia	ME Mahler (PI), JL Cummings, et al (Co-Investigators) VA Merit Review Grant; 1987 - 1990 ($124,000).
HIV-Related CNS Abnormalities	W Van Gorp (PI), CJ Frederich (Co-PI), JL Cummings et al (Co-Investigators) VA Research Program; 1987 - 1990 ($266,500).
Tardive Dyskinesia: Electromechanical Measures ($76,000).	JL Cummings (PI), W Wirshing, R Liber (Co-Investigators) Merit Review Award; VA Research Program; 1988 - 1990
Dementia and Geriatric Behavioral Neurology Research Fellowship	D Frank Benson, Director; JL Cummings, Co-Director NIA Training Grant, 1988 - 2002, Director, 1995 - 2002.
Mental illness in the elderly: diagnostic testing	A Leuchter, PI; JL Cummings et al, Co-Investigators NIA ROl MH 4070504; 1989 - 1996.
Depression in dementia of the Alzheimer type	J Cummings, PI; French Foundation Grant; 7/1/89 - 6/30/90 ($30,000).

PET studies in persons at risk for Alzheimer's disease	G Small, PI; JL Cummings et al, Co-Investigators, State of California 1989 - 1990 ($50,000)
Cholinergic treatment of behavioral disturbances in Alzheimer's disease	J Cummings (sponsor), DG Gorman (Co-Investigator) French Foundation for Alzheimer's Research; 7/1/90 - 6/30/92 ($30,000/year).
PET studies in persons at risk for Alzheimer's disease	G Small, PI; JL Cummings et al (Co-Investigators) NIMH FIRST Award; 1990 - 1995.
VA Geriatric Neurology Fellowship	J Cummings, PI; Funding for training of 2 Neurologists in Geriatric Neurology; 1992 - 1996.
UCLA Alzheimer's Disease Research Center	J Cummings, PI; National Institute on Aging 1991 - 2009.
Los Angeles Area Alzheimer Outreach	J Cummings, PI; National Institute on Aging 1992 - 1997; ($100,000/year).
Neuropsychiatric Inventory	J Cummings, PI; Irving and Helga Cooper Award for Geriatrics Research 1993 - 1994 ($20,000)
UCLA Alzheimer's Disease Research Center of California	J Cummings, PI; State of California. 1998 - recurring
Mental illness in aging: early diagnosis	G Small, PI; and JL Cummings, Co-PI, NIMH, 1990 - 1996 R 29 MH 46424-05

Industry-Sponsored Research and Clinical Trials:

Acetyl-l-carnitine in Alzheimer's disease	JL Cummings, PI; Double-blind efficacy trial sponsored by Sigma Tau Pharmaceutical Company; 1991 - 1993.
DuP 996 in Alzheimer's disease	JL Cummings, PI; Open label safety study sponsored by DuPont-Merck Pharmaceutical Company; 1991 - 1993.
Amyloid precursors in CSF and serum in Alzheimer's disease	J Cummings and B Miller, Co-PI's; Investigation of CSF and serum amyloid precursors; Athena Neuroscience; 1991 - 1993.
Cognex Access Program	JL Cummings, PI; Safety study of tacrine sponsored by Parke-Davis; 1992 - 1994.
Ondansetron in Alzheimer's disease	JL Cummings, PI; Double-blind study sponsored by Glaxo Pharmaceuticals; 1994.
Metrifonate in Alzheimer's disease	JL Cummings, PI; Double-blind study sponsored by Miles-Bayer; 1995.
Milameline in Alzheimer's disease	JL Cummings, PI; Double-blind study sponsored by Miles-Bayer; 1995 - 1996.
Zoloft for agitation in Alzheimer's disease	JL Cummings, Co-PI; Double-blind study sponsored by Pfizer; 1997 - 1999.
Donepezil for behavioral disturbances in nursing home patients.	JL Cummings and Stacey Wood, Co-PI's; Double-blind study sponsored by Pfizer; 1996 - 1998.

Cross-sectional study of Alzheimer's disease.	JL Cummings, PI: Pharmaco-economic study sponsored by Pfizer; 1996 - 1997.
Xanomeline in Alzheimer's disease.	JL Cummings, Co-PI; Double-blind study sponsored by Lilly; 1996 - 1998.
Olanzapine in Alzheimer's disease	JL Cummings, Co-PI; Double-blind study sponsored by Lilly; 1996 - 1998.
ENA-713 in Alzheimer's disease	JL Cummings, PI; Open-label study sponsored by Novartis; 1997 - 1998.
Aricept in vascular dementia	JL Cummings, PI; Double-blind and open-label study sponsored by Eisai; 1998 - present.
Exelon in nursing home patients	JL Cummings, PI; Open-label study of Exelon in patients in nursing homes Novartis; 1997 - 1998.
Cognitive, behavioral, and metabolic responses to metrifonate	JL Cummings, PI; Open-label study sponsored by Bayer; 1998 - 1999.
Donepezil Hcl (E2020) in Patients With dementia associated with MCI	JL Cummings, PI; A 30-week, open-label study sponsored by Esai; 1998 – 2001.
PET imaging responses to Galantamine treatment	JL Cummings, PI; study sponsored by Janssen; 2001 – 2003.
Neotrofin in patients with probable AD	JL Cummings, PI; placebo-controlled study sponsored by Neurotherapeutics; 2001 – 2002.
SR57746A in mild to moderate AD	JL Cummings, PI; randomized, double blind, placebo-controlled trial sponsored by Sanofi-Synthelabo; 2001 – 2002.
CX516 in MCI	JL Cummings, PI; study sponsored by Cortex, Inc.; 2002 – 2003.
Donepezil for memory impairment in PD	JL Cummings, PI; study sponsored by Pfizer, Inc. 1999 – 2002.
Behavior, Cognition, function and quality of life	JL Cummings, PI; Belmont Village; 2002 - 2005.
Biomarkers	JL Cummings, PI; study sponsored by SynX; 2003 – 2004.
Efficacy and Safely of Aricept in MCI	JL Cummings, PI; study sponsored by Pfizer / Eisa; 2003 – 2006.

FOUNDATION AND ALZHEIMER'S DISEASE COOPERATIVE STUDY TRIALS

Testosterone in AD and normal Controls	JL Cummings, Co-PI; Double-blind study sponsored by the French Foundation; 1999 - present.
Melatonin for sleep disturbance	JL Cummings, Co-PI; Multicenter trial sponsored by ADCS; 1998 - present.
Melatonin for sleep disturbance in AD	JL Cummings, PI; A multicenter, placebo-control study sponsored by ADCS/NIH; 1998 - 2000.

Minimum cognitive impairment	JL Cummings, Co- PI; Double-blind study sponsored by ADCS; 1999 - present.
Rofecoxib/Naproxen in patients in patients with AD	JL Cummings, Co-PI; Multicenter trial sponsored by ADCS; 1999 - present.
Vitamin E and donepezil to Prevent clinical progression In MCI	JL Cummings, PI; study sponsored by ADCS; 1999-2004.
MCI - normal instrument study	JL Cummings; PI; normal instrument study sponsored by ADCS; 1999-2004.
MCI – Imaging sub-study	JL Cummings, PI; Imaging sub-study sponsored by the ADCS 1999 – 2004.
Testosterone in males with AD and normal elderly males	JL Cummings, PI; placebo-control study sponsored by the ISOA and the French Foundation; 1999 – 2002.
Phase III trial of Rofecoxib and Naproxen in AD	JL Cummings, PI; study sponsored by the ADCS; 2000 – 2001.
Divalproate sodium for agitation in dementia	JL Cummings, PI; study sponsored by the ADCS; 2000 – 2002.
Primary prevention instrument protocol	JL Cummings, PI: study sponsored by ADCS; 2001 – 2006.
Treatment of agitation and psychosis in dementia/Parkinsonism	JL Cummings, PI; study sponsored by the ADCS' 2003 – 2004.
Simvistatin to slow the progression of AD	JL Cummings, PI; multicenter, randomized double blind, placebo-controlled study sponsored by the ADCS; 2003 – 2005.
Capacity to consent	JL Cummings, PI; study sponsored by the ADCS; 2003 – 2004.
Homocysteine to slow the rate of cognitive decline in AD	JL Cummings, PI; study sponsored by the ADCS; 2003 – 2005.
Curcumin in AD	JL Cummings, PI; pilot study sponsored by ISOA/French Foundation; 2003 – 2005.
Valproate to attenuate progression of AD	JL Cummings, PI; study sponsored by the ADCS; 2003 – 2005.

CONSULTANT TO INDUSTRY:

Bayer	1994 – 2000
Bristol-Myers Squibb	1999 – 2003
Cognishunt	2003 – 2004 (Safety Monitor)
Glasko SmithKline	2002 – 2003 (Data Safety Monitoring Committee)
Lundbeck International	2004
Memory Pharm	2004
Parke-Davis	1993 – 1997
Sandoz	1995
Searle	1999
Synx-pharm	2002 – 2004
Voyager	2001 – 2004
Wyeth	2004
Zeneca	1997
AstraZeneca	1999 – Present

Aventis	2003 – Present
Best Practice Consulting	2003 – Present
Biomedisyn	2001 – Present
Council of Advisors	2003 – Present (advise to investment bankers)
Eisai	1998 – Present
Genentech	2005 – Present
Janssen	1997 – 2004
Lilly	1995 – Present (Global Neuroscience Advisory Board)
Myriad	2004 – Present
Neurochem	2004 – Present (Chair DSMB)
Neurotrax	2005 - Present
Novartis	1998 – Present Alzheimer's Disease Advisory Board Parkinson's Disease Dementia Advisory Board Assisted in preparation of dossier on PD dementia for FDA
Ono	2000 – Present
Pfizer	1996 – Present (Alzheimer's Disease Advisory Board)
Praecis	2003 – Present

INDUSTRY RELATED ROLES:

Data Safety and Monitoring Board (Chair/Member)
Alzheimer's Disease Advisory Board (Chair/Member)
Global Advisory Board (Member)
Consultant to drug development team
Editor for manuscripts
Author of manuscripts
Poster author/presenter
Create/present one-day conference on clinical trials
Lecturer, industry preceptorship
Investigator's meeting instrument trainer
Newsletter advisor/editor

PUBLICATIONS:

Books

1. Cummings JL, Benson DF. Dementia: A Clinical Approach. Butterworths, Boston, 1983. (Japanese translation 1986; Chinese translation 1987).

   Second Edition (1992).

   Third Edition (2003). Mendez MF, Cummings JL.

2. Cummings JL. Clinical Neuropsychiatry. Grune and Stratton, New York, 1985.

3. Cummings JL, Miller B, (eds). Treatment and Long-Term Management of Alzheimer's Disease. Marcel Dekker, New York, 1990.

4. Cummings JL, (ed). Subcortical Dementia. Oxford University Press, New York, 1990.

5. Huber SJ, Cummings JL, (eds). Parkinson's Disease: Neurobehavioral Aspects. Oxford University Press, New York, 1992.

6. Coffey CE, Cummings JL, eds. Textbook of Geriatric Neuropsychiatry. American Psychiatric Press, Washington, D.C., 1994. (Italian translation 2001).

   Second edition (2000).

7. Cummings JL, Trimble MR. Concise Guide to Neuropsychiatry and Behavioral Neurology. American Psychiatric Press, Washington, D.C., 1995. (Japanese translation 1996)

   Second edition (2002); Turkish translation (2004)

8. Trimble ML, Cummings JL. Contemporary Behavioral Neurology. Butterworth's Heinemann, Boston, 1997.

9. Salloway S, Malloy P, Cummings, JL, (eds). The Neuropsychiatry of Limbic and Subcortical Disorders. American Psychiatric Press, Washington, DC, 1997.

10. Miller BL, Cummings JL (eds). The Human Frontal Lobes: Functions and Disorders. Guilford Press, New York, 1999.

11. McKeith I, Cummings JL, Lovestone S, Harvey R, Wilkinson D. Outcome Measures in Alzheimer's Disease. Martin Dunitz, London, 1999.

12. Bogousslavsky J, Cummings JL (eds). Behavior and Mood Disorders in Focal Brain lesions. Cambridge University Press, Cambridge, England, 2000.

13. Gauthier S, Cummings JL (eds). Alzheimer's Disease and Related Disorders Annual. Martin Dunitz, London, 2000.

14. Lichter D, Cummings JL (eds). Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders. The Guilford Press, New York, 2001.

15. Gauthier S, Cummings JL (eds). Alzheimer's Disease and Related Disorders Annual. Martin Dunitz, London, 2001.

16. Gauthier S, Cummings JL (eds). Alzheimer's Disease and Related Disorders Annual. Martin Dunitz, London, 2002.

17. Cummings JL. Neuropsychiatry of Alzheimer's Disease and Related Dementias. Martin Dunitz, London, 2003.

18. Cummings JL, Mega M. Neuropsychiatry and Behavioral Neuroscience. Oxford University Press, New York, 2003.

19. Gauthier S, Sheltons P, Cummings JL (eds). Alzheimer's Disease and Related Disorders Annual. Martin Dunitz, London, 2005.

20. Cummings JL, Hardy J, Poncet M, Christen Y (Eds). Genotype-Proteotype-Phenotype Relationships in Neurodegenerative Diseases, Series: Research and perspectives in Alzheimer's disease. Springer; Germany, 2005.

21. Gauthier S, Scheltens P, Cummings JL (eds). Alzheimer's Disease and Related Disorders Annual , 5. Taylor & Francis, London, 2006.

    Spanish Translation: Gauthier S, Scheltens P, Cummings JL. Enfermedad de Alzheimer y Trastornos Relacionados. Ars Medica, Barcelona, 2006.

22. Cummings JL ED). Progress in Neurotherapeutics and Neuropsychopharmacology. Cambridge University Press, United Kingdom, London 2006.

Yearbook of Geriatrics and Gerontology

1. Beck JC, Abrass I, Burton J, Small G, Cummings JL, Makinodon T (eds). Yearbook of Geriatrics and Gerontology 1988. Year Book Medical Publications, New York, 1988.

2. Beck JC, Abrass I, Burton J, Small G, Cummings JL, Makinodon T (eds). Yearbook of Geriatrics and Gerontology 1989. Year Book Medical Publications, New York, 1989.